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"*I would have everie man write what he knowes and no more.*"—MONTAIGNE

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# EDITORIAL

## ETHICS IN PUBLISHING

In January 1978, editors from some major biomedical journals published in English met in Vancouver, British Columbia, and drew up technical requirements for manuscripts to be submitted to these journals. The Vancouver group evolved into the International Committee of Medical Journal Editors (ICMJE), which in 1981 revised the requirements and published a second edition in 1982, and a third edition in 1988 [1]. While the *Uniform Requirements* describe mainly the way in which a manuscript should be prepared, they also make important recommendations on some ethical aspects: notably prior and duplicate publication, authorship, financial relationships posing conflict of interests, and requirements that procedures were conducted in accordance with the ethical standards of the appropriate committee on human experimentation or with the Helsinki Declaration.

More specifically with respect to duplicate publication, in the *Uniform Requirements* it is stated that most journals do not wish to consider for publication a paper describing work that has already been reported elsewhere or that has been submitted or accepted for publication elsewhere. (This does not preclude considering a paper that has been rejected by another journal or a complete report of a preliminary communication.) When submitting a paper, an author should always make a full statement about all submissions and previous reports that might be regarded as prior or duplicate publication of the same or very similar work, and copies of such material should be included with the submitted paper.

As the *Uniform Requirements* are not immediately available to most authors, many journals, including ANESTHESIOLOGY, ANESTHESIA AND ANALGESIA, ANAESTHESIA and BRITISH JOURNAL OF ANAESTHESIA, publish an individual *Guide to Contributors* which summarizes these findings and describes specific requirements. In our *Guide to Contributors*, it is stated clearly that papers submitted must not have been submitted to or published *in whole* or *in part* in any other journal. Despite these well publicized strictures, there have been several examples in the past two years wherein material published in or submitted to one of our journals has been either simultaneously submitted to or published in a second anaesthesia journal.

An example of duplicate publication which authors may think acceptable but which we invariably reject, comprises the use of control data to compare with one situation in one journal and the same control data compared against a second circumstance in a paper submitted to another journal. When authors fail to indicate in their list of references that material is "in press", or published recently in another journal, one conclusion is that the authors are deliberately practising deception.

For the past eight years, an International Meeting of Editors of Anaesthetic Journals has been convened at two-year intervals coinciding with either a European or World Congress of Anaesthesiology. At the most recent Fourth Meeting held in association with the Eighth European Congress of Anaesthesiology in Warsaw in 1990, there was some discussion of ethical problems in publishing. The most common and obvious problem discussed was that of duplicate submission and publication. This may be classified broadly into two types:

1. Reproduction in one journal of data identical to those published elsewhere with either similar or differing discussions. This is clearly unacceptable and represents a breach of copyright. Authors should be aware of the fact that reproduction of *blocks* of text, tables or figures always necessitates permission of both authors and editors.
2. The use of identical control data in two different papers, as noted above.

An additional issue of concern is the submission of various aspects of one single study to several different journals. Although this does not represent multiple publication *per se*, it nonetheless represents publication of an unnecessary number of papers and detracts from the interpretation of single manuscripts. All the editors present at the Fourth International Meeting of Anaesthetic Editors in *Warsaw, 1990*, were opposed to this type of practice and would request that all data from a single circumscribed study be submitted to one journal.

This international collaboration is illustrated by the fact that this joint editorial is appearing simultaneously in ANESTHESIOLOGY, ANESTHESIA AND ANALGESIA, BRITISH JOURNAL OF ANAESTHESIA and ANAESTHESIA. The views expressed on duplicate publication are also supported fully by David Bevan, who is publishing a similar editorial in this month's issue of the CANADIAN JOURNAL OF ANAESTHESIA, and also by John Roberts, who will be referencing this article in an editorial in ANAESTHESIA AND INTENSIVE CARE.

Improving communication between the editors of biomedical journals should facilitate detection of any failure of authors to follow the recommendations of the ICMJE and we hope that authors become aware of and exercise their responsibilities related to submission of manuscripts. Research published in biomedical journals must be held to the highest standards and adherence to ethical standards in publishing is an absolute expectation of our readers and of the public.

*Graham Smith*, B.SC., M.D., F.C.ANAES.
Editor, BRITISH JOURNAL OF ANAESTHESIA
*Ronald Miller*, M.D.
Editor in Chief, ANESTHESIA AND ANALGESIA
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Editor in Chief, ANESTHESIOLOGY
*M. Morgan*, F.C.ANAES.
Editor, ANAESTHESIA

### REFERENCE

1. International Committee for Medical Journal Editors. Uniform Requirements for Manuscripts Submitted to Biomedical Journals. *British Medical Journal* 1988; **296**: 401–405.

*British Journal of Anaesthesia* 1991; **66**: 423–432

# INFLUENCE OF AGE ON ATELECTASIS FORMATION AND GAS EXCHANGE IMPAIRMENT DURING GENERAL ANAESTHESIA

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## SUMMARY

*We have studied the effects of anaesthesia on atelectasis formation and gas exchange in 45 patients of both sexes, smokers and non-smokers, aged 23–69 yr. None of the patients showed clinical signs of pulmonary disease, and preoperative spirometry was normal. In the awake patient, partial pressure of arterial oxygen* ($Pa_{O_2}$) *decreased with increasing age* ($P < 0.001$) *and the alveolar–arterial oxygen partial pressure difference* ($PA_{O_2} - Pa_{O_2}$) *increased with age* ($P < 0.001$)*. Shunt, assessed by the multiple inert gas elimination technique, was small (mean 0.5%) and uninfluenced by age. However, there was an increasing dispersion (log* SD *Q) of ventilation/perfusion ratios* ($\dot{V}A/\dot{Q}$) *and increasing perfusion of regions of low* $\dot{V}A/\dot{Q}$ ($\dot{V}A/\dot{Q} < 0.1$) *with increasing age* ($P < 0.001$ *and* $P < 0.05$*, respectively). No patient displayed any atelectasis as assessed by computed x-ray tomography of the chest. During inhalation anaesthesia (halothane or enflurane) with mechanical ventilation, 39 of 45 patients developed atelectasis and shunt. There was a strong correlation between the atelectatic area and the magnitude of shunt* ($r = 0.81$, $P < 0.001$)*. Atelectasis and shunt did not increase significantly with age, whereas log* SD *Q and perfusion of regions with low* $\dot{V}A/\dot{Q}$ *ratios did* ($r = 0.55$, $P < 0.001$ *and* $r = 0.35$, $P < 0.05$*, respectively). Awake, the major determinant of* $Pa_{O_2}$ *was perfusion of regions of low* $\dot{V}A/\dot{Q}$ *ratios, which increased with age. During anaesthesia shunt influenced* $Pa_{O_2}$ *most, low* $\dot{V}A/\dot{Q}$ *being a secondary factor which, however, was increasingly important with increasing age, thus explaining the well-known age-dependent deterioration of arterial oxygenation during anaesthesia.*

***KEY WORDS***

*Anaesthesia, general Complications age, atelectasis Lung atelectasis, gas exchange*

Pulmonary gas exchange is impaired during anaesthesia (for a review see [1]). It is also generally held that the gas exchange impairment in anaesthetized subjects increases with age [1–4]. The causes of the gas exchange impairment during anaesthesia have not been fully understood. However, more recently we have identified at least one mechanism that contributes to impaired arterial oxygenation during anaesthesia—densities in dependent lung regions as assessed by computed x-ray tomography of the chest [5, 6]. These densities have been interpreted as atelectasis [5, 6], and they appear to produce shunt [7]. The dense regions, subsequently termed atelectasis, were independent of the subject's age in a previous report on 28 patients [8]. However, it is not known if shunt increases with age, or if gas exchange is affected by age in another way. In the present study, we have reviewed our previously collected data of clinically lung healthy subjects of different ages. The pooling of these data created a large enough base to allow regression analysis with respect to age.

## PATIENTS AND METHODS

During a 2-year period, 45 patients (participating in studies related to the present one from [7, 9, 10 and recently finished studies that have not yet

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TABLE I. *Patient characteristics. *Smokers: mean 16 (*SD *8) g tobacco day$^{-1}$ and 18 (14) pack-years. FVC = forced vital capacity; $FEV_1$ = forced expiratory volume in 1 s*

| | Age (yr) | Sex (M/F) | Weight (kg) | Height (m) | Non-smokers /Smokers | FVC (% of expected) | $FEV_1$/FVC (% of expected) |
|---|---|---|---|---|---|---|---|
| Mean | 46.3 | 36/9 | 75 | 1.77 | 23/22* | 109 | 94 |
| SD | 12.6 | | 8.1 | 0.07 | | 11.6 | 8.0 |

been published]) undergoing elective abdominal surgery were studied immediately before and during general anaesthesia. There were 36 men and nine women, aged 23–69 yr (mean 46 yr). Twenty-three of the patients had never smoked, 18 were smokers (light to moderate), and the remaining four patients were ex-smokers (table I). All patients were clinically healthy, and all had normal body configuration. Spirometry on the day before the study was normal in all: that is, the recorded spirometry data were within 2 SD of expected values [11]. Informed consent to all studies was obtained from the patients concerned and approval was granted by the Ethics Committee of Huddinge University Hospital.

### *Anaesthesia*

All patients received atropine 0.5 mg i.v. before induction of anaesthesia. No other premedication was given. Anaesthesia was induced with thiopentone 300–400 mg and fentanyl 0.10 mg i.v., followed by inhalation anaesthetics (0.8–1.0 % enflurane or 0.6–0.8 % halothane, inspired maintenance concentration) in oxygen–nitrogen (mean $F_{I_{O_2}}$ 0.40 (range 0.32–0.45)). To facilitate tracheal intubation, the patient received suxamethonium 75–100 mg i.v. Neuromuscular block was maintained by pancuronium given as a priming dose of 6–8 mg followed by intermittent doses of 2 mg i.v. when needed. After tracheal intubation, the lungs were ventilated mechanically at a rate of 12 b.p.m. (Servo 900 C ventilator equipped with an infra-red carbon dioxide analyser, $CO_2$ Analyzer 930, Siemens). Minute ventilation was adjusted to maintain an end-tidal carbon dioxide concentration of approximately 4%. Ventilatory volumes and airway pressures were obtained from the ventilator.

### *Catheterization and gas exchange*

Pulmonary artery (Swan–Ganz 7–French gauge, Edward's Laboratories) and brachial artery catheters were inserted for pressure recordings (reference: mid thoracic level) and blood sampling. Cardiac output was measured by thermodilution, and gas exchange was assessed by blood-gas analysis and measurement of the ventilation/perfusion ratios ($\dot{V}_A/\dot{Q}$) by multiple inert gas elimination technique. For this purpose, a solution of six gases (sulphur hexafluoride, ethane, cyclopropane, enflurane or halothane, diethyl ether and acetone) was infused into a vein. After steady state conditions had been obtained, arterial and mixed venous blood samples were taken and mixed expired gas was collected for subsequent analysis by gas chromatography. Arterial and mixed venous oxygen and carbon dioxide tensions ($Pa_{O_2}$, $P\bar{v}_{O_2}$, $Pa_{CO_2}$, $P\bar{v}_{CO_2}$) were measured by standard techniques, corrected to a standardized body temperature of 37 °C and the alveolar–arterial oxygen partial pressure difference ($PA_{O_2} - Pa_{O_2}$) was calculated. Venous admixture ("shunt" in a three-compartment analysis—the ideal, the "shunt" and the deadspace compartment) was calculated on the oxygen content in arterial, mixed venous and pulmonary end-capillary blood (the latter assumed to be equal to alveolar $P_{O_2}$), according to Riley [12]. Deadspace measured by the multiple inert gas elimination technique ($V_D$, $\dot{V}_A/\dot{Q}$ ratios > 100) includes apparatus deadspace both awake (approximately 20 ml) and during anaesthesia (approximately 40 ml). (For further details, see [7, 9, 10].)

### *Computed tomography of the chest*

The transverse lung area and the structure and density of the lungs were studied by x-ray computed tomography (CT), with the subjects in the supine position on the tomograph table (Somatom 2, Siemens). The arms were raised above the head to allow passage through the gantry (hole) in the CT scanner. This manoeuvre has no effect on FRC as tested in awake volunteers [13]. A frontal scout view covering the chest was obtained initially. Two CT scans in the transverse plane were performed, the lowermost at a level just above the top of the diaphragm and the other 5 cm cephalad. The same scan levels, relative to the spine, were used during the succeeding measurements during anaesthesia. Densities, considered to reflect atelectasis, were identified in dependent lung regions and were expressed in per cent of the total intrathoracic area (including mediastinum). (For further details, see [7, 9, 10].)

### *Procedure*

The catheters were introduced in the catheterization laboratory, and infusion of inert gases was started. The patient was then moved to the x-ray department and after 20 min of complete rest (40 min of infusion) recordings of central haemodynamic and gas exchange variables were made while the patient was breathing air. CT scans were obtained and the patient was anaesthetized. After 15 min of enflurane or halothane in oxygen–nitrogen anaesthesia and neuromuscular block, the haemodynamic and gas exchange variables were recorded and the CT scans repeated.

After the study the patients, while still anaesthetized, were moved to the operating theatre. All recordings were made with the patient in the supine position, awake or anaesthetized.

### *Statistics*

Mean values and standard deviation (SD) were calculated, except for the variable remaining sum of squares (RSS) where median and range were used because of uneven distribution of values. The significance of a difference was tested by paired Student's *t* test. Correlation and multiple stepwise linear regression were used to analyse relationships between different variables.

## RESULTS

### *Comparison between awake and anaesthesia*

Mean data on central haemodynamics, gas exchange and chest dimensions (including atelectasis) for all patients awake and during anaesthesia are shown in table II. Circulatory variables and arterial blood-gas tensions were within normal limits in the awake state [14, 15, local reference values]. Cardiac output and systemic arterial pressures were reduced significantly during anaesthesia to about 70–85 % of the awake value. A small (1–2 mm Hg) decrease in mean pulmonary arterial pressure was observed also.

Shunt (perfusion of regions with $\dot{V}_A/\dot{Q} < 0.005$) increased from 0.5 % of cardiac output awake to about 5 % during anaesthesia (table II). Log SD $Q$, defined as the logarithmic standard deviation of $\dot{V}_A/\dot{Q}$ around the mean $\dot{V}_A/\dot{Q}$ of the perfusion distribution, increased by almost 50 % during anaesthesia. This indicates an increased dispersion of $\dot{V}_A/\dot{Q}$ (increased $\dot{V}_A/\dot{Q}$ mismatch). Perfusion of regions of low $\dot{V}_A/\dot{Q}$ ($0.005 < \dot{V}_A/\dot{Q} < 0.1$) also increased significantly. Venous admixture was 5.5 % of cardiac output awake and almost doubled during anaesthesia. Awake venous admixture correlated best with perfusion of low

TABLE II. *Haemodynamic, gas exchange and CT data awake and during anaesthesia* (n = *45*). *HR = Heart rate;* $F_{I_{O_2}}$ = *inspired oxygen fraction;* $\dot{V}_E$ = *minute volume; Shunt and low* $\dot{V}_A/\dot{Q}$ = *perfusion of non-ventilated* ($\dot{V}_A/\dot{Q} < 0.005$) *and poorly ventilated* ($0.005 < \dot{V}_A/\dot{Q} < 0.1$) *regions, respectively; High* $\dot{V}_A/\dot{Q}$ = *ventilation of poorly perfused regions* ($10 < \dot{V}_A/\dot{Q} < 100$); $V_D$ = *ventilation of deadspace* ($\dot{V}_A/\dot{Q} > 100$); *Log SD* Q = *log SD of perfusion;* $Pa_{O_2}$, $Pa_{CO_2}$ = *arterial partial pressures of oxygen and carbon dioxide, respectively;* ($PA_{O_2} - Pa_{O_2}$) = *alveolar–arterial oxygen partial pressure difference. Significantly different from awake:* *$P < 0.05$; ***$P < 0.001$.

| Variable | Awake | Anaesthesia |
|---|---|---|
| Cardiac output (litre min$^{-1}$) | 6.3 (1.1) | 5.3 (0.8)*** |
| HR (beat min$^{-1}$) | 67 (10) | 79 (10)*** |
| Vascular pressures (mm Hg) | | |
| Systemic arterial, mean | 99.1 (13.3) | 72.0 (12.7)*** |
| Pulmonary artery, mean | 14.2 (3.0) | 13.5 (2.7)*** |
| Pulmonary capillary wedge | 8.1 (2.4) | 7.3 (2.2)* |
| Right atrial | 5.1 (2.5) | 5.3 (1.9) |
| Cross-sectional chest area (cm$^2$) | | |
| Scan 1 (top of diaphragm) | 377 (41) | 358 (41)*** |
| Scan 2 (5 cm cephalad of 1) | 355 (45) | 318 (46)*** |
| Atelectatic area (% intrathoracic area) | | |
| Scan 1 (top of diaphragm) | 0 | 1.9 (2.1)*** |
| Scan 2 (5 cm cephalad of 1) | 0 | 1.4 (1.7)*** |
| Gas exchange | | |
| $F_{I_{O_2}}$ | 0.21 (0.0) | 0.40 (0.05)*** |
| $\dot{V}_E$ (litre min$^{-1}$) | 8.4 (2.9) | 6.2 (1.1)*** |
| Shunt (% $\dot{Q}_t$) | 0.5 (1.0) | 4.8 (4.1)*** |
| Low $\dot{V}_A/\dot{Q}$ (% $\dot{Q}_t$) | 1.7 (3.3) | 5.0 (4.9)*** |
| High $\dot{V}_A/\dot{Q}$ (% $\dot{V}_E$) | 0.1 (0.3) | 1.8 (3.8)* |
| $\dot{V}_D$ (% $\dot{V}_E$) | 34.8 (14.1) | 35.0 (9.9) |
| Log SD $Q$ | 0.67 (0.28) | 1.04 (0.36)*** |
| Venous admixture | 5.5 (4.4) | 9.2 (4.9)*** |
| Arterial blood-gas values | | |
| $Pa_{O_2}$ (kPa) | 12.5 (1.7) | 21.4 (6.4)*** |
| $Pa_{CO_2}$ (kPa) | 4.9 (0.6) | 4.9 (0.7) |
| ($PA_{O_2} - Pa_{O_2}$) (kPa) | 1.4 (1.2) | 10.8 (6.6)*** |

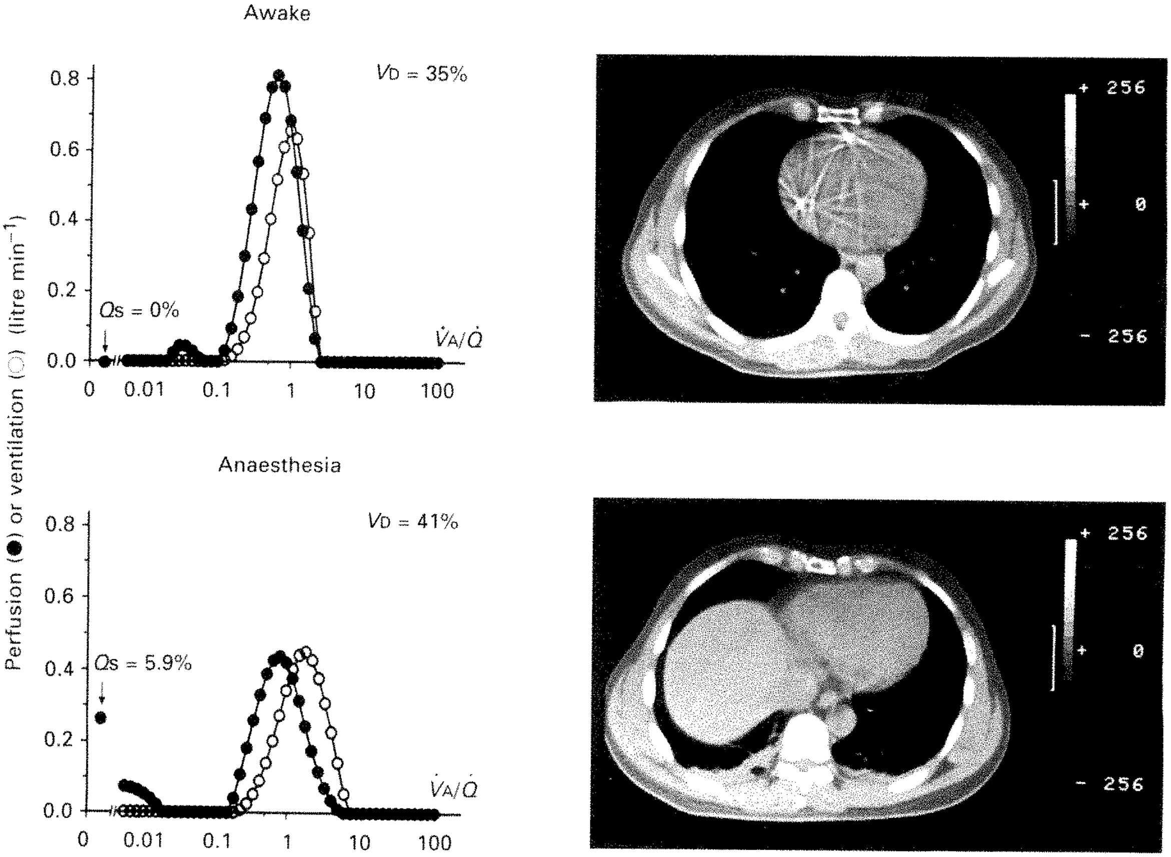

FIG. 1. Normal pattern of gas exchange and CT scans (caudal level) awake and during anaesthesia. Ventilation–perfusion distribution to the left; CT scan of the chest to the right. Note the increase in shunt, log SD $Q$ (widened $\dot{V}\text{A}/\dot{Q}$ mode), and low $\dot{V}\text{A}/\dot{Q}$, in addition to the atelectatic areas in the dorsal part of the CT scan during anaesthesia. The large white area in the middle of the right hemithorax (lower CT scan) is the diaphragm that has moved cranially during anaesthesia.

$\dot{V}\text{A}/\dot{Q}$ regions (venous admixture = 0.54 (low $\dot{V}\text{A}/\dot{Q}$)+4.65; $r = 0.40$; $P < 0.01$), and during anaesthesia the best correlation was with the sum of both shunt and perfusion of low $\dot{V}\text{A}/\dot{Q}$ regions (venous admixture = 0.67 (shunt+low $\dot{V}\text{A}/\dot{Q}$)+2.73; $r = 0.83$; $P < 0.001$). Arterial oxygenation was impaired during anaesthesia, as demonstrated by the increased $(P\text{A}_{\text{O}_2} - P\text{a}_{\text{O}_2})$. (However, the increased $F\text{I}_{\text{O}_2}$ during anaesthesia is an additional confounding factor.)

A decrease in the cross-sectional thoracic area of approximately 5% was noted after induction of anaesthesia. Awake, no patient had evidence of atelectasis. During anaesthesia, 39 of 45 patients developed densities in dependent lung regions, interpreted as atelectasis (fig. 1). In patients with atelectasis in the caudal CT scan, more than 80% also had atelectasis in the cranial scan. No patient displayed atelectasis solely in the cranial scan, but always in combination with atelectasis in the caudal scan. The atelectatic area was slightly larger in the caudal CT scan than in the cranial (table II). The magnitude of shunt correlated strongly with the atelectatic area, and calculations made on the caudal CT scan are shown in figure 2.

When the data were classified into smokers (including the four ex-smokers) ($n = 22$) and non-smokers ($n = 23$), no difference in any variable could be disclosed. Also, smoking was not a significant factor in a multivariate analysis which also included age. Separate data for the two groups have therefore not been presented in this paper. There was also no significant difference in any circulatory or gas exchange variable between the two anaesthetics (halothane and enflurane).

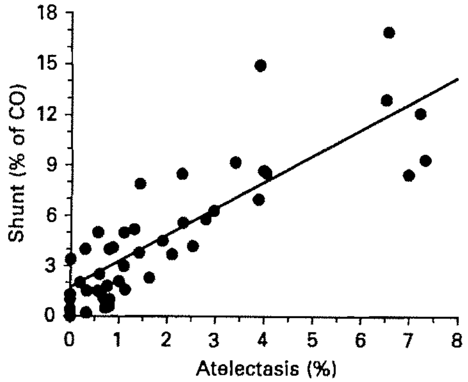

FIG. 2. Atelectatic area (% of intrathoracic area, caudal scan level) and shunt (% of cardiac output (CO)) during anaesthesia. Regression equation: Shunt = 1.6Atelectatic area +1.7; $r = 0.81$, $P < 0.001$.

*Influence of age*

*Circulation.* Awake, both systemic and pulmonary artery pressures increased with age (correlations and regression line equations in table III), but pulmonary capillary wedge and right atrial pressures, in addition to cardiac output, were not affected significantly. During anaesthesia, systolic pulmonary artery pressure increased significantly with age ($r = 0.46$, $P < 0.05$), but no other age-dependent correlations were found.

*Gas exchange.* There was no significant correlation between age and shunt. There were positive correlations for the awake state between age and log SD $Q$ and age and perfusion of regions of low $\dot{V}\text{A}/\dot{Q}$ ($r = 0.55$, $P < 0.001$ and $r = 0.39$, $P < 0.01$, respectively) (fig. 3, regression equations in table III). Venous admixture increased with age at the same rate as perfusion of regions of low $\dot{V}\text{A}/\dot{Q}$. A fair correlation between age and $Pa_{O_2}$ ($r = -0.44$, $P < 0.01$) was found (fig. 4, regression line equation in table III). If the analysis was extended to the combination of age, perfusion of regions with low $\dot{V}\text{A}/\dot{Q}$, $P\bar{v}_{O_2}$ and $Pa_{CO_2}$ on the one hand, and $Pa_{O_2}$ on the other, the correlation increased further ($r = 0.83$, $P < 0.001$) (regression equation in table III). ($PA_{O_2} - Pa_{O_2}$) also showed a correlation with age ($r = 0.50$, $P < 0.001$). The correlation increased if not only age, but also $P\bar{v}_{O_2}$ and perfusion of regions with low $\dot{V}\text{A}/\dot{Q}$ ratios were included in the analysis ($r = 0.71$, $P < 0.001$) (regression equation in table III).

In the anaesthesia state, there were correlations between age and log SD $Q$ ($r = 0.52$, $P < 0.01$) (fig. 3, regression equation in table III), between age and perfusion of regions of low $\dot{V}\text{A}/\dot{Q}$ ($r = 0.35$, $P < 0.05$) (table III), and between age and venous admixture ($r = 0.42$, $P < 0.05$) (table III). The age coefficients (slopes of the regression lines) were similar to those in the awake state, but the intercepts were higher during anaesthesia. Shunt did not show any correlation with age. $Pa_{O_2}$ decreased with age, and did so faster than in the awake state (however, $FI_{O_2}$ differed between awake and anaesthesia, as mentioned earlier) ($r = -0.50$, $P < 0.01$) (fig. 4, regression equation in table III). There was a corresponding increase in ($PA_{O_2} - Pa_{O_2}$) with age ($r = 0.34$, $P < 0.05$) (table III). An extension of the analysis, taking into account not only age but also perfusion of regions of low $\dot{V}\text{A}/\dot{Q}$ shunt, $P\bar{v}_{O_2}$, $FI_{O_2}$ and $Pa_{CO_2}$ on the one hand, and $Pa_{O_2}$ on the other, increased the correlation to such an extent that 75% of the variation in $Pa_{O_2}$ could be explained ($r = 0.88$, $P < 0.001$). The same variables, except $Pa_{CO_2}$, explained the variation in ($PA_{O_2} - Pa_{O_2}$) to a similar degree ($r = 0.91$, $P < 0.001$) (regression equations in table III). Mixed venous oxygen tension did not correlate with age, nor did arterial-mixed venous oxygen partial pressure difference.

*Atelectasis and chest dimensions.* Age did not influence the amount of atelectasis, or the decrease in cross-sectional chest area during anaesthesia.

## DISCUSSION

The large data base used in the present study enabled us to demonstrate that both atelectasis and shunt developed to a substantial degree during anaesthesia, but that neither atelectasis nor shunt increased with increasing patient age. On the other hand, the dispersion of the $\dot{V}\text{A}/\dot{Q}$ distribution, indicating the degree of $\dot{V}\text{A}/\dot{Q}$ mismatch, increased with increasing age, both in the awake state and during anaesthesia. Thus increasing $\dot{V}\text{A}/\dot{Q}$ mismatch with age adds to the age-independent formation of atelectasis and shunt, to produce the well known gas exchange impairment during anaesthesia.

*Methodological aspects*

Two complicated techniques have been used: the multiple inert gas elimination technique in order to enable separation of shunt from $\dot{V}\text{A}/\dot{Q}$ mismatch and formation of low $\dot{V}\text{A}/\dot{Q}$ regions,

TABLE III. *Correlations and regression lines for arterial pressures and gas exchange variables* (n = 45). $FI_{O_2}$ = *inspired oxygen fraction; Shunt and low* $\dot{V}A/\dot{Q}$ = *perfusion of non-ventilated* ($\dot{V}A/\dot{Q} < 0.005$) *and poorly ventilated* ($0.005 < \dot{V}A/\dot{Q} < 0.1$) *regions, respectively; Log* SD Q = *log* SD *of perfusion*; $Pa_{O_2}$, $Pa_{CO_2}$ = *arterial partial pressures of oxygen and carbon dioxide, respectively*; ($PA_{O_2}-Pa_{O_2}$) = *alveolar–arterial oxygen partial pressure difference*

| | | | |
|---|---|---|---|
| **Age and arterial pressures** | | | |
| *Systemic arterial pressures (mm Hg)* | | | |
| Awake | | | |
| Systolic | = 0.5Age+115 | $r = 0.37$ | $P = 0.05$ |
| Mean | = 0.3Age+83 | $r = 0.33$ | $P < 0.05$ |
| **Age and gas exchange** | | | |
| $Pa_{O_2}$ (*kPa*) | | | |
| Awake | $Pa_{O_2} = -0.06\text{Age}+15.3$ | $r = -0.44$ | $P < 0.01$ |
| Anaesthesia | $Pa_{O_2} = -0.25\text{Age}+33.3$ | $r = -0.50$ | $P < 0.001$ |
| ($PA_{O_2}-Pa_{O_2}$) | | | |
| Awake | $(PA_{O_2}-Pa_{O_2}) = 0.05\text{Age}-0.83$ | $r = 0.50$ | $P < 0.001$ |
| Anaesthesia | $(PA_{O_2}-Pa_{O_2}) = 0.18\text{Age}+2.40$ | $r = 0.34$ | $P < 0.05$ |

| | | | |
|---|---|---|---|
| *Pulmonary artery pressure (mm Hg)* | | | |
| Awake | | | |
| Systolic | = 0.2Age+14 | $r = 0.49$ | $P < 0.01$ |
| Mean | = 0.01Age+10 | $r = 0.38$ | $P < 0.05$ |
| Anaesthesia | | | |
| Systolic | = 0.1Age+12 | $r = 0.46$ | $P < 0.05$ |
| *Log* SD Q | | | |
| Awake | Log SD Q = 0.012Age+0.12 | $r = 0.55$ | $P < 0.001$ |
| Anaesthesia | Log SD Q = 0.015Age+0.35 | $r = 0.52$ | $P < 0.001$ |
| *Low* $\dot{V}A/\dot{Q}$ (*% of cardiac output*) | | | |
| Awake | Low $\dot{V}A/\dot{Q}$ = 0.14Age−3.0 | $r = 0.39$ | $P < 0.05$ |
| Anaesthesia | Low $\dot{V}A/\dot{Q}$ = 0.14Age−1.5 | $r = 0.35$ | $P < 0.05$ |
| *Venous admixture (% of cardiac output)* | | | |
| Awake | Ven. admixt = 0.15Age−1.5 | $r = 0.43$ | $P < 0.01$ |
| Anaesthesia | Ven. admixt = 0.17Age+1.6 | $r = 0.42$ | $P < 0.01$ |

| | | | |
|---|---|---|---|
| **Multiple regression for $Pa_{O_2}$ and ($PA_{O_2}-Pa_{O_2}$)** | | | |
| $Pa_{O_2}$ (*kPa*) | | | |
| Awake | $Pa_{O_2} = -0.04\text{Age}-0.11\ (\text{low}\ \dot{V}A/\dot{Q})+1.05\ P\bar{v}_{O_2}-1.60Pa_{CO_2}+16.45$ | $r = 0.83$ | $P < 0.001$ |
| Anaesthesia | $Pa_{O_2} = -0.08\text{Age}-0.99\text{Shunt}-0.47\ (\text{low}\ \dot{V}A/\dot{Q})+2.63P\bar{v}_{O_2}-2.00Pa_{CO_2}+56.26FI_{O_2}-4.11$ | $r = 0.88$ | $P < 0.001$ |
| ($PA_{O_2}-Pa_{O_2}$) (*kPa*) | | | |
| Awake | $(PA_{O_2}-Pa_{O_2}) = 0.03\text{Age}+0.10\ (\text{low}\ \dot{V}A/\dot{Q})-0.82P\bar{v}_{O_2}+4.39$ | $r = 0.71$ | $P < 0.001$ |
| Anaesthesia | $(PA_{O_2}-Pa_{O_2}) = 0.08\text{Age}+0.94\text{Shunt}+0.45\ (\text{low}\ \dot{V}A/\dot{Q})-2.63P\bar{v}_{O_2}+42.27FI_{O_2}-1.60$ | $r = 0.91$ | $P < 0.001$ |

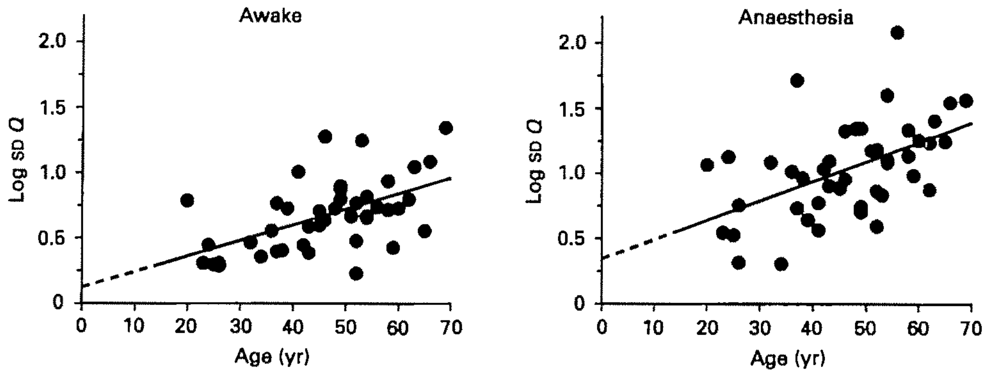

FIG. 3. Age and log SD $Q$ awake and during anaesthesia. A significant difference was found in intercept, but not in slope, between the awake state and during anaesthesia ($P < 0.01$). For regression equations and correlations, see table III.

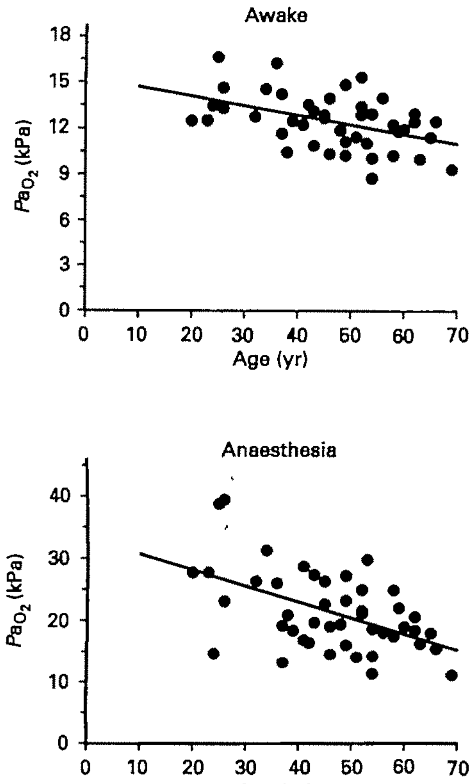

FIG. 4. $Pa_{O_2}$ against age in the awake state ($FI_{O_2} = 0.21$) and during anaesthesia ($FI_{O_2} = 0.40$). For regression equations and correlations, see table III.

and computed x-ray tomography of the chest to demonstrate and quantify atelectasis.

Ventilation-perfusion distribution in the lungs has been analysed with several different techniques, from the initial three-compartment analysis of venous admixture, physiological deadspace and the ideal compartment by Riley and co-workers [12], to the multi-compartment analysis by multiple inert gas elimination technique by Wagner and co-workers [16, 17]. The theoretical and methodological aspects of the multiple inert gas elimination technique have been investigated extensively. It has been concluded that up to three distinct $\dot{V}A/\dot{Q}$ modes and shunt can be detected [16–18], and the reliability of the ventilation–perfusion distribution has been studied by linear programming [19, 20]. A more cautious approach to the multiple inert gas elimination technique has also been advocated [21].

The quality of the inert gas data may be tested by calculating the remaining sum of squares (RSS) between measured (arterial and mixed venous samples) and calculated (from the derived $\dot{V}A/\dot{Q}$ distribution) retentions. RSS had a median of 2.5 (range 0.1–22.9) and it was less than 6 in 74 of a total of 90 measurements made both awake and during anaesthesia. This should be compared with a suggested requirement that 50% of the $\dot{V}A/\dot{Q}$ measurements should have a fit with an RSS less than 6 [22]. Thus the quality of the inert gas data seems to be satisfactory.

However, a good fit does not rule out other possible $\dot{V}A/\dot{Q}$ distributions from a given set of inert gas data. To test that a derived $\dot{V}A/\dot{Q}$ distribution is compatible with the measured oxygenation of the blood, the measured $Pa_{O_2}$ may be compared with that obtained from the derived $\dot{V}A/\dot{Q}$ distribution. This requires measurement of cardiac output, mixed venous oxygen tension and the slope of the haemoglobin dissociation curve.

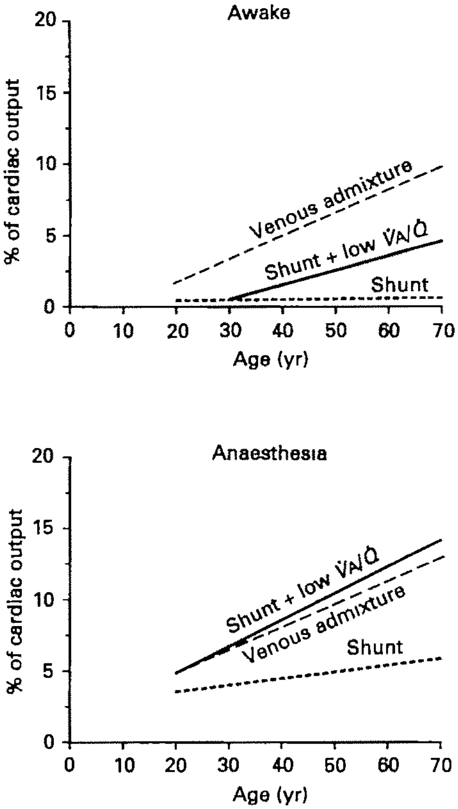

FIG. 5. Schematic drawing of shunt, the sum of shunt and perfusion of regions with low $\dot{V}_A/\dot{Q}$, and venous admixture against age awake and during anaesthesia. Note the appearance or increase of shunt during anaesthesia and the increasing perfusion of low $\dot{V}_A/\dot{Q}$ regions with age both awake and during anaesthesia. Also note the close similarity between venous admixture and the sum of shunt and low $\dot{V}_A/\dot{Q}$ during anaesthesia. Regression equations and correlations (see also table III): *Awake*—Shunt = 0.004Age+0.36, $r = 0.04$, ns; Shunt+low $\dot{V}_A/\dot{Q}$ = 0.104Age−3.0, $r = 0.41$, $P < 0.05$. *Anaesthesia*—Shunt = 0.047Age+2.6, $r = 0.14$, ns; Shunt+low $\dot{V}_A/\dot{Q}$ = 0.187Age+1.1, $r = 0.38$, $P < 0.05$.

These were measured or assumed (the dissociation curve) and, by using the algorithms of Kelman [23, 24], $Pa_{O_2}$ was estimated. The measured ($Pa_{O_2,meas}$) and calculated ($Pa_{O_2,calc}$) oxygen tension agreed well according to the equation:

$$Pa_{O_2,\,calc} = 1.07\ Pa_{O_2,\,meas} - 1.2\,(Pa_{O_2}\text{ in kPa})$$

$r = 0.96$; $P < 0.001$. The minor deviation from the identity line is to be expected, as the calculation of $Pa_{O_2,calc}$ does not take into account Thebesian blood flow (veins emptying in the left atrium). The good correlation is further support for the reliability of the $\dot{V}_A/\dot{Q}$ distributions found here.

The other complicated technique that deserves comment is analysis of atelectasis by computed tomography of the chest. The atelectatic area was identified by eye as a dense area in dependent lung regions. The area was encircled by hand and calculated by a computer. For comparative purposes, an analysis was made afterwards in 50 % of patients, by defining the atelectatic area as picture elements (pixels) with an attenuation of −100 to +100 Hounsfield units (HU). The computer-based analysis still required careful delineation of the lung tissue from the soft tissues of the chest wall, which have an attenuation factor which does not differ by more than 30–40 HU from that of the atelectatic lung. Computer analysis and manual analysis produced similar results for atelectatic areas (per cent of intrathoracic area: manual = 1.04 (computer analysis)−0.39; $r = 0.99$, $P < 0.001$). The variability between different measurements, expressed as coefficient of variation of duplicate measurements of the same scan, was no larger than 6 %.

### *Influence of age*

*Central circulation.* The correlations between age and systemic artery and pulmonary artery pressures in the awake state are in accordance with earlier observations [14]. During anaesthesia, familiar decreases in systemic vascular pressures and cardiac output were observed. In addition, a small but significant reduction of pulmonary artery pressure was found, which is in accordance to the findings of Price and colleagues [25]. However, no or only weak correlations with age were noted during anaesthesia.

*Arterial oxygenation and ventilation/perfusion.* The decrease in $Pa_{O_2}$ with age in the awake state is in accordance with the results of Marshall and Whyche [26] who, in a review, calculated a regression line:

$$Pa_{O_2} = -0.04\text{ age} + 13.6\ (\text{age in years and } Pa_{O_2}\text{ in kPa})$$

(*cf.* our regression line in table III). Correlation analysis of the present data showed that age, as inferred from $r^2$, accounted for approximately 15–20 % of the changes in $Pa_{O_2}$ awake. Multiple regression analysis showed that 67 % of the alterations in $Pa_{O_2}$ were explained by age, perfusion of regions with low $\dot{V}_A/\dot{Q}$ ratios, $Pa_{CO_2}$ and $P\bar{v}_{O_2}$. Shunt was minor or absent, and had no significant influence on $Pa_{O_2}$.

During anaesthesia, most patients developed atelectasis, and they also developed shunt, which accounted for approximately 20% of the variation in $Pa_{O_2}$ ($r = 0.46$) and almost 50% of that in ($PA_{O_2} - Pa_{O_2}$) ($r = 0.69$). The dispersion of $\dot{V}\mathrm{A}/\dot{Q}$ distribution (log SD $Q$) explained another 15–20% ($r = 0.37$–$0.45$) of these variations.

Neither atelectasis nor shunt increased with age, whereas both log SD $Q$ and low $\dot{V}\mathrm{A}/\dot{Q}$ did. It is also worth noting that both log SD $Q$ and perfusion of low $\dot{V}\mathrm{A}/\dot{Q}$ regions increased with age at the same rate during anaesthesia as in the awake state, but at greater values. Thus there was a parallel shift of regression lines. The effect of these parallel shifts was that anaesthesia increased the dispersion of $\dot{V}\mathrm{A}/\dot{Q}$ ratios (log SD $Q$) to the same extent as an increase in age by approximately 20 yr, and it increased perfusion of low $\dot{V}\mathrm{A}/\dot{Q}$ regions as much as an increase in age by 10 yr.

The effect of age on shunt, perfusion of low $\dot{V}\mathrm{A}/\dot{Q}$ regions and venous admixture has been presented schematically in figure 5. It may be seen that shunt was the major cause of impaired arterial oxygenation during anaesthesia in younger patients but, around 45 yr, the amount of perfusion of low $\dot{V}\mathrm{A}/\dot{Q}$ regions equals the shunt and, at greater ages it becomes larger than the shunt. However, the scatter around the regression line (age *vs* low $\dot{V}\mathrm{A}/\dot{Q}$) was large, precluding the use of these relations for predictions in any individual. Also, it should be remembered that shunt blood flow has a greater impact on arterial desaturation than perfusion of low $\dot{V}\mathrm{A}/\dot{Q}$ regions, in particular when the patient undergoes ventilation of the lungs with oxygen-enriched gas mixtures (for a review, see West [27]). Calculation of venous admixture from blood-gas values and alveolar partial pressure of oxygen according to the standard equation, includes both shunt ($\dot{V}\mathrm{A}/\dot{Q} < 0.005$) and $\dot{V}\mathrm{A}/\dot{Q}$ mismatch (in particular "low $\dot{V}\mathrm{A}/\dot{Q}$"), but to a varying extent depending on, among other things, $FI_{O_2}$. There was a close similarity between venous admixture and the sum of shunt and low $\dot{V}\mathrm{A}/\dot{Q}$ during anaesthesia, whereas venous admixture was larger than shunt and low $\dot{V}\mathrm{A}/\dot{Q}$ in the awake state. This difference may be attributed to larger influence of $\dot{V}\mathrm{A}/\dot{Q}$ mismatch (not only low $\dot{V}\mathrm{A}/\dot{Q}$) when breathing air (awake state), than breathing oxygen-enriched gas (anaesthesia) [27].

There is also support in the literature of an increasing $\dot{V}\mathrm{A}/\dot{Q}$ mismatch with increasing age during anaesthesia. Thus Rehder and co-workers [28] found only a small log SD $Q$ in anaesthetized young healthy volunteers, and also very little shunt. Prutow and colleagues [29], however, found a larger shunt in similarly young group of patients, the mean shunt being around 8%. In middle-aged subjects, Bindslev and colleagues [30] found a widened $\dot{V}\mathrm{A}/\dot{Q}$ distribution with a greater log SD $Q$ than that reported by Rehder and co-workers in young volunteers [28]. Shunt averaged 8%, similar to that reported by Prutow and co-workers. Finally, Dueck and colleagues detected even larger broadening of the $\dot{V}\mathrm{A}/\dot{Q}$ distributions and increases in shunt in old patients with varying degrees of pulmonary disease [18]. Thus there appears to be an increase in the $\dot{V}\mathrm{A}/\dot{Q}$ mismatch with increasing age, when data from these four studies are combined. This is in accordance with earlier observations of increasing gas exchange impairment (increasing venous admixture) with age during anaesthesia [1–4].

While shunt appears to be explained by the formation of atelectasis in dependent lung regions during anaesthesia, the cause of increased log SD $Q$ and increased perfusion of regions with low $\dot{V}\mathrm{A}/\dot{Q}$ ratios is unexplained. One possible explanation is airway closure in lung regions just above the atelectatic zone. Increased airway closure, as assessed by single breath nitrogen washout and bolus techniques, has been demonstrated by several groups [31–33], but conflicting results have also been reported [34, 35]. Moreover, the techniques used can not easily differentiate between airway closure and atelectasis if collapsed tissue is recruited during the vital capacity manoeuvre that is part of the airway closure measurement. Airway closure during anaesthesia is therefore still an open question. Further studies are required to answer this question.

## ACKNOWLEDGEMENTS

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# CRANIO–CAUDAL MOVEMENT OF THE STERNUM ON INDUCTION OF ANAESTHESIA

M. R. LOGAN AND G. B. DRUMMOND

**SUMMARY**

*The cranio–caudal movement of the sternum was studied by the technique of video magnification during induction of anaesthesia with thiopentone 2–4 mg $kg^{-1}$ i.v. in 20 patients. Anaesthesia produced no consistent change in end-expiratory position of the sternum; there was a range of movement from 3.1 mm cephalad to 5.4 mm caudad. There was a significant relationship between movement and degree of obesity of the patient ($P < 0.01$), with the sternum tending to caudal movement in the obese patient.*

**KEY WORDS**

*Anaesthetics, intravenous. thiopentone Anaesthetic techniques · induction, sternal movement*

Induction of anaesthesia has been shown to be associated with a decrease of 0.2–2.5 litre in the volume of the lung at end-expiration (functional residual capacity, FRC) [1–3]. One potential contribution to this decrease may be the reduction of ribcage inspiratory muscle tone that occurs on induction of anaesthesia [4]. In conscious patients, small doses of neuromuscular blocking drugs abolish activity of the intercostal muscles [5] and reduce FRC. Although the scalene muscles are often considered to be only accessory muscles of respiration, they are active during normal breathing [6, 7], and the action of the scalene and inspiratory ribcage muscles is to displace the sternum in a cranial direction. The present study was designed to evaluate the displacement of the end-expiratory position of the sternum on induction of anaesthesia.

## PATIENTS AND METHODS

After Ethics Committee approval had been granted, informed consent was obtained from 20 female patients (ASA I and II) (table I).

The patients received temazepam 20 mg orally 1 h before induction of anaesthesia. The patient was allowed to relax in a supine position on a mattress filled with polystyrene beads (Howmedica Vac-Pac). Air was evacuated from the mattress to make a conforming mould to minimize movement of the patient's axial skeleton during induction of anaesthesia. A video camera (Hitachi 6P-61M) on maximum zoom magnification was

TABLE 1. *Sternal tidal excursion and displacement of the end-expiratory sternal position after induction of anaesthesia. + = Cranial displacement; − = caudal displacement*

| Patient No. | Height (cm) | Weight (% of expected) | Sternal tidal excursion (mm) | Post-induction sternal displacement (mm) |
|---|---|---|---|---|
| 1 | 155 | 89 | 10 | +3.1 |
| 2 | 176 | 107 | 12 | −0.4 |
| 3 | 153 | 154 | 5.5 | −5.4 |
| 4 | 163 | 120 | 3.5 | −3.3 |
| 5 | 160 | 82 | 3 | +0.9 |
| 6 | 150 | 87 | 5.5 | +2.4 |
| 7 | 165 | 115 | 6 | +1.7 |
| 8 | 163 | 81 | 7 | −3.9 |
| 9 | 175 | 74 | 7 | −3.0 |
| 10 | 153 | 109 | 3 | +1.5 |
| 11 | 167 | 122 | 7 | −1.7 |
| 12 | 156 | 116 | 4 | −1.3 |
| 13 | 162 | 92 | 4 | +0.4 |
| 14 | 145 | 86 | 7 | +0.7 |
| 15 | 160 | 120 | 7 | −2.6 |
| 16 | 171 | 87 | 6 | +0.2 |
| 17 | 163 | 80 | 2 | +1.7 |
| 18 | 151 | 132 | 4 | −3.1 |
| 19 | 165 | 94 | 5 | +1.5 |
| 20 | 152 | 95 | 6 | −1.3 |

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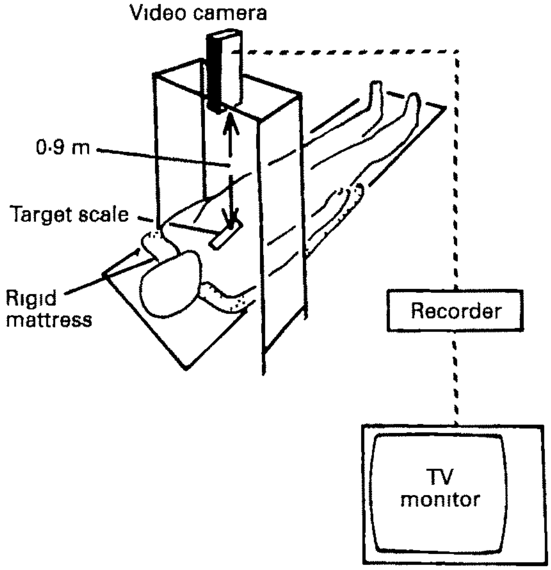

FIG. 1. Arrangement of the camera gantry.

positioned on a rigid frame 0.9 m above a 150-mm linear ruler taped to the patient's sternum with its scale in the cranio–caudal axis (fig. 1). The camera's shortest focal distance of 0.9 m allowed the camera to act as its own rangefinder to an accuracy of ±3 mm on maximum zoom. The ruler was secured to the most horizontal portion of the sternum in such a way that the scale was at right angles to the camera axis at end-expiration.

The patient was allowed as long as necessary to relax and achieve a stable state of quiet breathing before the video recording was started. Ten normal breaths were recorded before anaesthesia was induced with thiopentone 2–4 mg $kg^{-1}$ injected over 30–60 s until loss of the eyelash reflex. Oxygen 100% was administered through a Magill breathing system via a facemask while it was ensured that airway obstruction did not occur by observation of the reservoir bag for unimpeded respiratory or cardiac movement. The recording was continued until 10 regular consecutive quiet breaths were recorded after induction.

The video image of the ruler was played back on a 66-cm monitor screen (Barco 2634) resulting in a linear magnification of 5.4 times. By using the technique of frame stop analysis, the end-tidal position of the ruler was taken to be that of the average of six consecutive quiet breaths both before and after induction. Measurements were made from the monitor screen using a single line of sight to the centre of the screen, to eliminate the possibility of parallax errors. A mark was made on the monitor screen at the end-expiratory position which was taken as the most caudal point of the sternal movement. The scale of the ruler image was used to determine the displacement of the ruler at the end-tidal position after induction of anaesthesia.

To assess the accuracy of the monitor system, a micrometer gauge was used to simulate movements of the same target in the range found in the clinical study. Similar video recordings and measurements were made of these movements. The measurements made corresponded precisely to the simulated movements, with an accuracy of ±0.2 mm (SD).

Data were analysed statistically by least squares linear regression [8]. Ideal patient weights were predicted on the basis of sex, age and height [9].

## RESULTS

There was no consistent direction of movement of the end-expiratory position of the sternum on induction of anaesthesia (mean −0.6 mm, SD 2.4 mm) (table I). The change in end-expiratory position of the sternum ranged from 3.1 mm cephalad to 5.4 mm caudad. There was a significant relationship ($P < 0.01$) between the direction of sternal movement and the degree of obesity of the patient (weight/ideal weight %) (fig. 2): most overweight patients had a caudal sternal movement, whereas in those who were underweight the sternum tended to move cephalad.

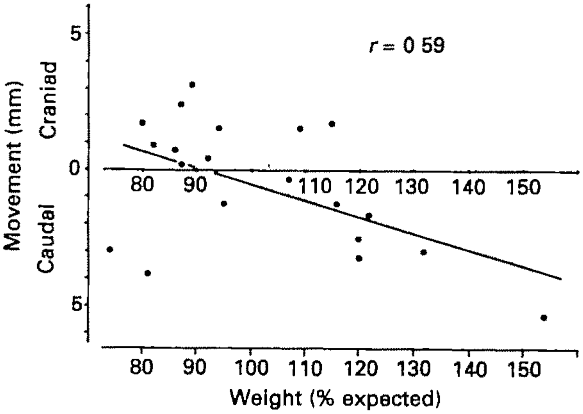

FIG 2. Comparison of the sternal displacement and degree of obesity (weight/ideal weight %). $r = 0.59$; $P < 0.01$.

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## DISCUSSION

The technique of video magnification uses an enlarged image of a linear scale to measure distances. All the measurements are subject to an equivalent magnification factor. This arrangement eliminates errors that could be introduced by antero–posterior sternal movement on the magnification factor, and at the same time increases the accuracy of the system. Changes in distance between the camera and the ruler alter both scale size and measurable movement by the same factor.

The ruler was fixed over the sternum at right angles to the camera axis at the preoperative end-expiratory position to minimize parallax errors. Rotation of the sternum in the sagittal plane would create a shortening of the ruler scale image. Although rotation was not measured in this study, simple geometry predicts that even a 10° rotation, which is considerable, would shorten the apparent scale by only 2 %.

Video magnification, being an optical technique, has the advantage over methods using magnetometry, inductive plethysmography and strain gauges, because it has no physical attachment to the surface of the body. This prevents mechanical interaction between the patient and the transducer.

In a previous study, using stereophotogrammetry [10], the polystyrene bead mattress, used in the present study, was shown to hold the axial skeleton virtually motionless. Although this could not be verified in this study because of the camera's narrow field of view, the mattress was used in an identical technique by the same investigators. Consequently, all movements detected were unlikely to be caused by movements of the body frame. No recording of tidal volume was taken to ensure that sternal movements were in phase with ventilation. Some subjects breathing normally in the supine position may show a slight degree of phase difference between ribcage and abdomen during inspiration and expiration, but at end-expiration both parts of the chest wall are at their minimum dimension [11]. However, no asynchrony or paradoxical movement was observed in the chest wall after induction of anaesthesia.

It is now generally accepted that the reduction in FRC that occurs on induction of anaesthesia is the result of a complex interaction of changes in the configurations of the walls of the thoracic and abdominal cavities [12] and perhaps in the volume of blood within these cavities [13, 14].

Interpretation of changes in chest wall dimensions is made more complicated by the several degrees of freedom of the thorax. In addition to changes in ribcage and abdominal diameter or circumference, flexion and extension of the vertebral column may also alter chest wall volume. If the diameters of the ribcage and abdomen remain constant, flexion of the thoracolumbar spine reduces the volume contained by the chest wall [15]. Thoracolumbar flexion can be estimated by the distance from the sternum to the pubis after correction for ribcage movement, because ribcage movement also causes sternal movement with a vector in the cranio–caudal dimension. In previous studies of the effects of anaesthesia on the external dimensions of the thorax [16–18], no account was taken of possible changes in the position of the spine. In the present study, care was taken to ensure that the spine remained in as constant a position as possible. Consequently, motion of the sternum in a cranio–caudal direction in the present study would represent changes associated with inflation and deflation of the ribcage. However, we observed motion of the sternum in only a single plane, and this may only represent a vector of the true direction of the sternal movement. To characterize the motion of a body fully, it is necessary to know its translation (distance and direction of movement) and rotation (change in attitude about an axis of reference). The translation of the sternum on inspiration is usually anteriorly and cranially. Sternal rotation is more difficult to measure and may be more variable, depending on the relative expansion of the upper and lower parts of the ribcage. For example, Krayer and colleagues [19] showed that induction of anaesthesia was associated with variable changes in the cross-section of the upper and lower ribcage, indicating that the sternum could rotate as the ribcage volume was reduced. In that study, the number of subjects was small and the range of body build was small, making assessment of the influence of body build difficult.

The present study did not show a consistent caudal movement of sternal end-expiratory position. Subjects with greater than expected body weight showed a caudal sternal movement, whereas in those of less than expected weight the sternum tended to move towards the head. This might be explained by a possible difference in the vectors of antero–posterior and cranio–caudal movement. The sternum may have a different position and pattern of motion in the obese. It is also possible that overweight subjects have a greater degree of tonic inspiratory activity in the muscles that act to expand the upper ribcage, so that lung volume can be maintained in the supine position. Loss of activity on induction of anaesthesia [4] would result in caudal motion of the sternum. In morbidly obese subjects, the reduction in FRC that occurs on induction of anaesthesia is proportionally greater than in normal subjects [20]. It is interesting to note that patients whose weight was close to that expected showed virtually no change in their sternal end-expiratory resting positions. The pattern of sternal movements in this study agrees with weight-related changes in ribcage volume found in a previous study using stereophotogrammetry [10]. In that study, ribcage volume decreased in overweight patients and increased in underweight patients. Because most of the tidal volume in the resting supine subject is caused by movement of the abdominal compartment [12], it is not practicable to relate the movement of the sternum associated with ventilation in the present study, to the possible contribution of sternal movement to lung volume change caused by induction of anaesthesia.

In conclusion, induction of anaesthesia causes caudal motion of the anterior ribcage in overweight patients. Further studies are needed of several dimensions of the ribcage in order to assess correctly the volume change that occurs with onset of anaesthesia.

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# HYPOXAEMIA DURING ANAESTHESIA—AN OBSERVER STUDY

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## SUMMARY

*We have investigated 296 inpatients in a single-blind observer study to determine the incidence, degree and duration of hypoxaemia during anaesthesia. The clinical recognition of hypoxaemia, period of time until recognition and risk factors were studied. Oxygen saturation ($Sp_{O_2}$) was monitored continuously with a pulse oximeter (Ohmeda, model 3700). One or more episodes of mild hypoxaemia ($Sp_{O_2}$ 86–90%) were recorded in 53% of patients. Severe hypoxaemia with $Sp_{O_2}$ values $< 81\%$ were recorded in 20% of patients. The mild hypoxaemic episodes lasted up to 34.6 min (mean 2.3 min) and 70% were not detected by the anaesthetist. In the remaining 30% of episodes, the anaesthetist diagnosed the complication with a mean time delay of 70 s. After intervention a mean time delay of 57 s was recorded until $Sp_{O_2}$ exceeded 90%. Utilizing a stepwise multiple logistic regression analysis, we found that risk factors associated with a greater incidence of hypoxaemia were patient age ($P < 0.005$) and anaesthetic technique ($P < 0.00001$). We conclude that hypoxaemic episodes in our operating rooms are common during anaesthesia and suggest preoxygenation in all patients in addition to administration of supplementary oxygen during arousal from anaesthesia and during transfer to the recovery room.*

***KEY WORDS***

*Complications hypoxaemia. Monitoring pulse oximetry.*

The occurrence and possible pathogenesis of hypoxaemia during anaesthesia were described several years ago [1–5]. In these early studies using discontinuous and invasive techniques, the exact occurrence of hypoxaemia was not described. With the development of the pulse oximeter it is now possible to measure oxygen saturation ($Sp_{O_2}$) continuously and non-invasively [6, 7]. This technique is accurate in the saturation range 75–100%, the range relevant to clinical anaesthesia [6–9].

The aim of this single-blind observer study was to investigate the incidence, degree and duration of hypoxaemia during routine anaesthesia using a continuous non-invasive monitoring technique. The number of undetected hypoxaemic episodes, the period of time until recognition of hypoxaemia and intervention, risk factors and causes of hypoxaemia were also recorded.

## PATIENTS AND METHODS

Oxygen saturation ($Sp_{O_2}$) of 86–90% was defined as mild hypoxaemia, $Sp_{O_2}$ of 81–85% as moderate hypoxaemia and $Sp_{O_2} < 81\%$ as severe hypoxaemia.

The responsible anaesthetist in the operating room was instructed to follow the normal guidelines of the department regarding patient care and safety. All patients were monitored in the usual manner with continuous electrocardiography (ECG), automatic measurement of arterial pressure and heart rate at least every 5 min and, when indicated by type of surgery or the general physical condition of the patient, central venous pressure (CVP). Fifty percent of the patients in the study were anaesthetized at Herlev University Hospital and the other 50% at Esbjerg Central Hospital. One pulse oximeter (Ohmeda model

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TABLE I. *Patient characteristics, duration of anaesthesia and surgery, and choice of drugs used for premedication and anaesthesia*

| | No. of patients (total = 296) | Mean | Median | Range |
|---|---|---|---|---|
| Age (yr) | | 52.1 | 53.0 | 18–91 |
| Body weight (kg) | | 71.3 | 69.0 | 40–136 |
| Height (cm) | | 167.1 | 170.0 | 136–203 |
| Duration of anaesthesia (min) | | 114.0 | 100.0 | 20–623 |
| Duration of surgery (min) | | 77.0 | 60.0 | 7–569 |
| Transfer time to the recovery room (min) | | 6.3 | 6.0 | 2–16 |
| Premedication | 276 | | | |
| Diazepam (mg) | 141 | 10.8 | 10.0 | 2.5–20.0 |
| Lorazepam (mg) | 86 | 2.3 | 2.5 | 1.25–4.5 |
| Pethidine (mg) | 11 | 57.3 | 50.0 | 25–100 |
| Morphine (mg) | 38 | 7.4 | 7.5 | 2.5–10.0 |
| Regional anaesthesia | 65 | | | |
| Spinal | 54 | | | |
| Extradural | 11 | | | |
| Sedation | | | | |
| Diazepam (mg) | 7 | 6.8 | 5.0 | 2.5–10.0 |
| Midazolam (mg) | 8 | 6.0 | 5.6 | 2.5–10.0 |
| Fentanyl (mg) | 6 | 0.12 | 0.10 | 0.05–0.30 |
| Ketamine (mg) | 4 | 86.3 | 72.5 | 50–150 |
| General anaesthesia | 231 | | | |
| I.v. | 129 | | | |
| Thiopentone (mg) | 125 | 304.1 | 300.0 | 100–600 |
| Diazepam (mg) | 7 | 8.2 | 7.5 | 5–10 |
| Midazolam (mg) | 11 | 6.5 | 5.0 | 2–10 |
| Doperidol (mg) | 106 | 9.9 | 10.0 | 5–20 |
| Fentanyl (mg) | 122 | 0.45 | 0.40 | 0.10–1.50 |
| Alfentanil (mg) | 7 | 1.2 | 1.0 | 0.5–2.0 |
| Inhalation | 102 | | | |
| Thiopentone (mg) | 97 | 362.4 | 350.0 | 100–850 |
| Diazepam (mg) | 5 | 7.0 | 5.0 | 3–13 |
| Fentanyl (mg) | 45 | 0.26 | 0.20 | 0.05–1.20 |
| Methadone (mg) | 45 | 6.1 | 5.0 | 3–13 |
| Neuromuscular block | | | | |
| Suxamethonium (mg) | 180 | 107.0 | 100.0 | 50–500 |
| Pancuronium (mg) | 144 | 5.2 | 5.6 | 0.4–20.6 |
| Atracurium (mg) | 54 | 35.0 | 30.0 | 2.5–80.0 |

3700) was used in each department. Data from the memory of the pulse oximeter were stored in a computer for further analysis. The patients studied were chosen at random by the investigators, according to a predetermined rotation schedule. Upon patient inclusion, the investigators were unaware of the physical status of the patient and the choice of anaesthetic.

We studied 296 inpatients (177 female), aged 18 yr or older, who were admitted for elective surgery under general, spinal or extradural anaesthesia and with an expected duration of surgery of more than 20 min (table I). Patients were undergoing ophthalmic, ENT, orthopaedic, gastric, urological and gynaecological operations. Exclusions included patients with a history of severe lung disease and a preoperative oxygen saturation $\leqslant 90\%$.

Observation and monitoring of oxygen saturation using the pulse oximeter was started immediately upon arrival in the operating theatre and continued until arrival in the recovery room (RR). One of five observers, all physicians with more than 2 years of anaesthesia practice, observed oxygenation continuously as recorded by the pulse oximeter. The display of the pulse oximeter was shielded from the anaesthetist and the theatre staff and the alarms were disconnected in order to ensure a blind study. If the pulse oximeter showed $Sp_{O_2} < 91\%$ for more than 20 s, the observer registered the facts and circumstances. If $Sp_{O_2}$ was 81–85 % for more than 3 min or decreased to < 81 %, the observer notified the anaesthetist and circumstances and intervention were registered. The duration of the hypoxaemic episodes and the period of time until recognition and intervention were timed with a stop-watch. A period of hypoxaemia was registered only if normal plethysmographic pulse wave was present on the display of the pulse oximeter. For each patient, the degree and the duration of hypoxaemia was confirmed later upon review of the computer recordings.

Phases of anaesthesia were classified as follows:
*Before induction:* the period after arrival of the patient in the operating theatre, but before administration of the induction agent or lumbar puncture.
*Induction:* from the start of the injection of the induction agent or lumbar puncture until surgical preparation.
*Maintenance:* from start of surgical preparation until end of operation.
*Arousal:* from end of operation to start of transportation to RR.
*Transfer to RR:* from start of transportation to arrival at RR, including the moving of the patient from the operating table to the bed.

The age, body weight, height, ASA physical status, anaesthetic technique and duration, surgical site and type of operation were noted for each patient. The medical records were reviewed for a history of respiratory disease, heart disease, hypertension or other co-existing diseases requiring constant medical treatment.

The anaesthetic technique was classified into two main groups, general anaesthesia and regional anaesthesia. Independent of the study, the anaesthetist responsible for the patients chose the anaesthetic technique, taking into consideration: the type of surgery, the patient's physical status and the patient's wishes. For premedication, the patient received either a benzodiazepine orally or an opioid i.m. 1 h before induction. General anaesthesia included one of two standard techniques: inhalation agent (enflurane, isoflurane or halothane), nitrous oxide in oxygen and fentanyl; or i.v. anaesthesia with nitrous oxide in oxygen. Pancuronium or atracurium was chosen for neuromuscular block. Residual neuromuscular block was antagonized with neostigmine and atropine. Regional anaesthesia consisted of either extradural or spinal anaesthesia. Supplementary oxygen 3 litre $min^{-1}$ was administered nasally to all patients receiving regional anaesthesia. Patients were not transferred from the operating theatre to the RR until their vital signs were stable and, for patients receiving general anaesthesia, after tracheal extubation. During transportation of the patient to the RR, supplementary oxygen was administered only if prescribed by the anaesthetist. Upon admission to the RR all patients received supplementary oxygen.

The study was approved by the Regional Ethics Committee for Copenhagen County, and informed consent was obtained from each patient.

All data were coded and checked for missing or inconsistent values. Upon entry in the database, the data for each patient were matched with those on the original data sheet. The incidence of hypoxaemia is reported in percent. Oxygen saturation and duration of hypoxaemia are reported as mean and median values plus range.

For each risk factor, the proportion of patients with at least one hypoxaemic episode was compared with those without hypoxaemia using a chi-square test or Goodman–Kruskal's gamma test. In order to eliminate errors caused by multiple comparison and to separate the roles of various risk factors, we applied a stepwise multiple logistic regression analysis. This analysis was performed only for mild hypoxaemia ($Sp_{O_2}$ 86–90 %). $P < 0.05$ was considered significant.

## RESULTS

Pulse oximeter monitoring was abandoned periodically in 21 (7 %) of the patients because of low peripheral perfusion resulting in "low quality signal" indication on the pulse oximeter (2 %), lack of patient co-operation (3 %) or electrical interference (2 %). The preoperative physical status of these patients did not differ significantly compared with the entire patient population in the study.

In 157 patients (53 %), one or more episodes of mild hypoxaemia ($Sp_{O_2}$ 86–90 %) were noted. $Sp_{O_2}$ 81–85 % was found in 34 % of the patients and values < 81 % were recorded in 20 % of patients (table II). A total of 392 hypoxaemic episodes occurred in the 157 mild hypoxaemic patients (table II); more than one hypoxaemic episode was registered in 59 % of the patients and 10 % of these experienced more than four episodes. The mild hypoxaemic episodes of the individual patient lasted up to 34.6 min (mean

TABLE II. *Number of patients with one or more episodes of hypoxaemia and number of hypoxaemic episodes per patient at the three values of saturation during all phases of anaesthesia and transfer to the recovery room. *Also counted among the 157 patients at $Sp_{O_2}$ 86–90%; †also counted among the 100 patients at $Sp_{O_2}$ 81–85%*

| $Sp_{O_2}$ (%) | Patients in category |  | No. of hypoxaemic episodes | No. of hypoxaemic episodes per patient |  |  |
|---|---|---|---|---|---|---|
|  | No. | (%) |  | Mean | Median | Range |
| 86–90 | 157 | 53 | 392 | 2.5 | 2 | 1–12 |
| 81–85 | 100* | 34 | 157 | 1.6 | 1 | 1–4 |
| < 81 | 58† | 20 | 76 | 1.3 | 1 | 1–3 |

2.3 min (table III)). Hypoxaemic episodes were found throughout all phases of anaesthesia (table III).

The presumed causes of hypoxaemia, as noted by the observers, were hypoventilation during spontaneous ventilation (63%), hypoventilation during controlled ventilation (14%), airway obstruction (14%) and others (7%).

In 55% of cases, the hypoxaemic episodes were not diagnosed by the anaesthetist. The observers notified the anaesthetist in 15% of the cases in accordance with the study procedure. In the remaining 30% of the episodes, the anaesthetist diagnosed the complication and intervened. The mean time interval from $Sp_{O_2}$ decrease to a value less than 91% and until recognition was 70 s (median 30 (range 1–800) s). The anaesthetists' diagnoses of hypoxaemia were based on clinical detection of, for example, hypoventilation, apnoea or cyanosis. In the 59 (15%) instances of hypoxaemia notified to the anaesthetist by the observer, the mean time interval between notification and the resulting intervention was 21 s (median 8 (range 1–300) s). Intervention consisted of an increase in $F_{I_{O_2}}$ (46%), increased ventilation (31%), airway adjustment (15%) and others (8%). The mean time interval from intervention to $Sp_{O_2} > 90\%$ was 57 s (median 27 (range 2–524) s).

Several patient-related and operative risk factors were revealed by use of the chi-square or Goodman–Kruskal's gamma test (table IV).

TABLE III. *Number of hypoxaemic episodes in the hypoxaemic patients and their duration during the different phases of anaesthesia at the three saturation values.* n = *No. of patients in group*

|  | Hypoxaemic episodes |  | Duration of hypoxaemic episodes (s) |  |  |
|---|---|---|---|---|---|
|  | No. | % | Mean | Median | Range |
| $Sp_{O_2}$ 86–90% ($n$ = 157) |  |  |  |  |  |
| Before induction | 20 | 5 | 185 | 103 | 30–837 |
| Induction | 96 | 24 | 81 | 40 | 20–564 |
| Maintenance | 58 | 15 | 208 | 95 | 22–2080 |
| Arousal | 82 | 21 | 160 | 69 | 20–2000 |
| Transfer to RR | 136 | 35 | 167 | 122 | 20–672 |
| Total | 392 | 100 | 139 | 82 | 20–2080 |
| $Sp_{O_2}$ 81–85% ($n$ = 100) |  |  |  |  |  |
| Before induction | 4 | 3 | 31 | 30 | 30–35 |
| Induction | 41 | 26 | 35 | 27 | 6–216 |
| Maintenance | 13 | 8 | 163 | 60 | 10–690 |
| Arousal | 43 | 27 | 122 | 67 | 4–265 |
| Transfer to RR | 56 | 36 | 81 | 54 | 4–400 |
| Total | 157 | 100 | 78 | 40 | 4–690 |
| $Sp_{O_2}$ < 81% ($n$ = 58) |  |  |  |  |  |
| Before induction | 2 | 2 | 15 | 15 | 10–20 |
| Induction | 19 | 25 | 27 | 19 | 5–180 |
| Maintenance | 6 | 8 | 86 | 35 | 5–300 |
| Arousal | 24 | 32 | 55 | 49 | 3–300 |
| Transfer to RR | 25 | 33 | 55 | 30 | 2–240 |
| Total | 76 | 100 | 43 | 25 | 2–300 |

TABLE IV. *Patient-related and operative risk factors of hypoxaemia. *Chi-square test or Goodman–Kruskal's gamma test at $Sp_{O_2}$ 86–90%. †Stepwise multiple logistic regression analysis at $Sp_{O_2}$ 86–90% for control of multiple comparisons and the fact that the risk factors are not exclusive §Statistics not performed because of relatively few patients in this category*

| | Total no. of patients | $Sp_{O_2}$ 86–90% (% of patients) | P* | P† | $Sp_{O_2}$ 81–85%§ (% of patients) | $Sp_{O_2}$ < 81§ (% of patients) |
|---|---|---|---|---|---|---|
| Heart disease | | | | | | |
| Yes | 43 | 65 | 0.09 | ns | 40 | 23 |
| No | 253 | 51 | | | 33 | 19 |
| Lung disease | | | | | | |
| Yes | 36 | 64 | 0.16 | ns | 32 | 5 |
| No | 260 | 52 | | | 34 | 21 |
| Hypertension | | | | | | |
| Yes | 30 | 70 | 0.049 | ns | 53 | 33 |
| No | 266 | 51 | | | 32 | 18 |
| ASA-status | | | | | | |
| I | 200 | 50 | 0.17 | ns | 30 | 18 |
| II | 66 | 58 | | | 39 | 18 |
| III | 27 | 67 | | | 48 | 33 |
| IV | 3 | 67 | | | 33 | 33 |
| Age (yr) | | | | | | |
| ⩽ 29 | 43 | 42 | 0.04 | 0.005 | 30 | 19 |
| 30–49 | 97 | 53 | | | 34 | 19 |
| 50–69 | 92 | 50 | | | 34 | 18 |
| 70 ⩽ | 64 | 66 | | | 36 | 22 |
| Duration of anaesthesia (min) | | | | | | |
| ⩽ 60 | 73 | 43 | 0.05 | ns | 22 | 12 |
| 61–120 | 116 | 51 | | | 31 | 18 |
| 121–180 | 70 | 66 | | | 49 | 21 |
| 181 ⩽ | 37 | 59 | | | 38 | 22 |
| Operation site | | | | | | |
| Eye and ENT | 33 | 61 | 0.01 | ns | 33 | 15 |
| Extremities | 59 | 58 | | | 42 | 29 |
| Lower abdomen | 147 | 43 | | | 24 | 14 |
| Upper abdomen | 40 | 65 | | | 50 | 28 |
| Breast | 17 | 77 | | | 53 | 24 |
| Operation size | | | | | | |
| Major | 98 | 57 | 0.08 | ns | 38 | 20 |
| Minor | 188 | 53 | | | 32 | 20 |
| Diagnostic | 10 | 20 | | | 20 | 10 |
| Anaesthetic technique | | | | | | |
| Regional | 63 | 33 | 0.0004 | 0.00001 | 16 | 8 |
| General | 233 | 59 | | | 39 | 23 |

When the stepwise multiple logistic regression analysis was applied, the significant risk factors were reduced to patient age ($P < 0.005$) and anaesthetic technique ($P < 0.00001$) (table IV).

## DISCUSSION

As a consequence of discontinuous measurements, the incidence and degree of hypoxaemia were not investigated in early studies on hypoxaemia during anaesthesia [1–5]. Another non-invasive continuous measuring technique, transcutaneous $P_{O_2}$, has been available many years [10, 11], but has never gained widespread use in studies on hypoxaemia during anaesthesia because of a relatively slow response to changes in $F_{I_{O_2}}$ and frequently inaccurate reflections of $Pa_{O_2}$ values [11, 12]. The continuous, non-invasive and accurate technique of pulse oximetry permits a more thorough study of hypoxaemia during anaesthesia. This study has demonstrated a high incidence of mild (53%) and severe (20%) hypoxaemic episodes widely distributed throughout all phases of anaesthesia. The anaesthetists recognized hypoxaemia in only 30 % of the cases, with a mean delay of 70 s. After intervention there was a mean time delay of 57 s until $Sp_{O_2} > 90\%$.

Several studies using pulse oximetry have focused on the incidence of hypoxaemia during transportation from the operating theatre to the RR [13–15]. The incidence of hypoxaemia in these studies was found to be 29–35 %, which agrees well with the findings from that part of our study dealing with transportation. In adults, the incidence of hypoxaemia during all phases of anaesthesia has been investigated only in a small number of outpatients undergoing minor gynaecological operations [16]. In this selected group, only 10 % of patients had hypoxaemic episodes. Coté and colleagues [17] discovered that in 76 children 24 major events ($Sp_{O_2} \leqslant 85\%$ for $\geqslant 30$ s) occurred during anaesthesia. The events were distributed throughout all phases of anaesthesia, as in the present study. Smith and Crul reported that oxygen desaturation (75–88 %) occurred in three of four patients given sedatives during regional anaesthesia without concomitant administration of oxygen [18].

Seventy percent of the hypoxaemic episodes in our study remained undetected by the anaesthetists—an observation in accordance with that made as early as 1947 by Comroe and Botelho [19] who stated that a "serious grade of arterial anoxemia may be unrecognized by many physicians...". This statement, in recent years, has been supported in several studies indicating that cyanosis and other clinical signs of hypoxaemia are unreliable, a conclusion we support [17, 20]. Even in the 118 hypoxaemic episodes recognized by the anaesthetist a long and, in our opinion, clinically important delay (mean 70 s) was recorded.

Despite the observer's intervention, the episodes with hypoxaemia lasted up to 11.5 min at $Sp_{O_2}$ 81–85 % and up to 5 min with $Sp_{O_2} < 81\%$ (table III). This was the result of a delay of up to 5 min before intervention by the anaesthetist after notification and the fact that, after intervention, up to 8.7 min may elapse before $Sp_{O_2}$ increases to greater than 90 %. Had the pulse oximeter been available to the anaesthetist, the early warning presumably would have elicited an early response.

Preoxygenation of the patients before induction of general anaesthesia was not performed as a routine procedure. All patients underwent ventilation briefly with 100 % oxygen before tracheal intubation, but several hypoxaemic episodes were observed shortly after the start of the i.v. injection of sedatives and opioids (table III). We believe that at least three of four hypoxaemic episodes during induction may have been avoided following careful preoxygenation. Several studies on emergency inductions have demonstrated that breathing 100 % oxygen for 3 min before induction nearly always eliminates hypoxaemia [21, 22].

The mean duration at all three grades of hypoxaemia was longer during maintenance of anaesthesia (table III). This may be explained by the fact that this was the longest study period, so unrecognized mild episodes would continue without interference. Furthermore, the anaesthetists might not have been so vigilant during this period of anaesthesia, as the risk of hypoxaemia is generally believed to be associated with induction and arousal.

Forty-seven percent of the hypoxaemic episodes were found during arousal after tracheal extubation and during transfer to the RR. Department standards require that all patients receive 100 % oxygen before extubation and should receive supplementary oxygen after extubation, but not as routine during transportation to the RR. In the minutes just after extubation, several procedures such as lifting the patient into bed, disconnection of i.v. cannulae, etc. were carried out. As a consequence, several hypoxaemic episodes occurred because of insufficient or disconnected supplementary oxygen. Our study was not designed to evaluate the efficiency of the supplementary oxygen prescribed in a few patients for transportation to the RR; previous studies during transportation to the RR have shown that the incidence of hypoxaemic episodes may be reduced to almost zero if supplementary oxygen is given [14, 23].

The observers suspected hypoventilation as a possible explanation in 77 % of the hypoxaemic episodes. Anaesthetic, opioid or neuromuscular blocking agents were suspected to have a major influence but, as in previous studies of the underlying causes of hypoxaemia, ventilation/perfusion maldistribution, airway closure, diffusion hypoxaemia, increased oxygen consumption and post-hyperventilation hypoxaemia may also play a major role [1–5, 24, 25]. Our study was not designed to distinguish between these factors.

Risk factors for hypoxaemia discovered in the current investigation were similar to those found in previous studies [4, 16, 20, 24]. Several risk factors were revealed by use of the chi-square test. In a stepwise multiple logistic regression analysis, however, only age and anaesthetic technique remained significant (table IV). Regional anaesthesia was accompanied by a significantly lower risk of hypoxaemia ($P < 0.00001$).

Our data raise several questions. Is hypoxaemia of the degree recorded dangerous to the patient, and would the routine use of a pulse oximeter, as advocated by several departments and anaesthesiological societies, reduce morbidity and mortality [26, 27]? From retrospective studies, we know that problems with oxygenation could be an important factor leading to increased morbidity and mortality [28, 29]. No prospective studies seem to have confirmed these theories. On the other hand, grave hypoxaemia is known to have serious consequences. Hypoxaemia, of the degree that we have found, has some physiological effects on the patient [30], but the clinical importance remains unknown.

We now know that, during routine anaesthesia, hypoxaemia is more common and severe than previously assumed. The hypoxaemic episodes are difficult to detect by clinical surveillance and, when recognized, their treatment is initiated with considerable delay. Consequently, we advocate routine preoxygenation for all patients and careful administration of supplementary oxygen during regional anaesthesia, during arousal from general anaesthesia and during transfer to the recovery room.

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# REVERSAL OF BENZODIAZEPINE SEDATION WITH THE ANTAGONIST FLUMAZENIL

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## SUMMARY

*The effectiveness of the benzodiazepine antagonist, flumazenil, was evaluated in a randomized double-blind clinical study in which diazepam 0.2 mg $kg^{-1}$ or midazolam 0.1 mg $kg^{-1}$ was used for i.v. sedation. We studied 120 day-case patients undergoing gastroscopy and treated with either flumazenil 0.1–2 mg or placebo after the procedure. Psychometric assessment of four aspects of recovery over a 3-h period showed that flumazenil attenuated the sedative effects of the benzodiazepines, but did not antagonize the sedation completely. For patients sedated with diazepam, there was a significant effect of flumazenil on speed of motor co-ordination after 90 min ($P < 0.01$), and for those given midazolam a similar effect was found at 20 min ($P < 0.01$). However, after 3 h all four groups of patients had not returned to baseline performance in accuracy of motor co-ordination ($P < 0.01$) and cortical arousal ($P < 0.05$), and the two groups sedated with diazepam still displayed memory deficits ($P < 0.05$). Flumazenil did not attenuate the subjective experience of sedation as measured by visual analogue scales. These results indicate that sedation is multidimensional, differentially affecting the hierarchy of cognitive functions. In day-cases, antagonism of benzodiazepine sedation with flumazenil would not hasten the safe discharge of patients.*

**KEY WORDS**

*Anaesthetic techniques intravenous sedation. Antagonists. flumazenil. Hypnotics· diazepam, midazolam. Recovery. psychomotor assessment*

The benzodiazepines diazepam and midazolam are often used for sedation for day-case patients undergoing gastroscopy. These two sedatives differ from each other not only in their rate of elimination and production of active metabolites, but also in the type of sedation they induce [1–3]. After administration of diazepam, patients may not appear to be as sedated as those given midazolam, but the effects produced may last longer [4, 5]. It has been shown that gastroscopy patients are often discharged whilst still experiencing residual sedative effects [6].

The clinical efficacy of the imidazobenzodiazepine derivative, flumazenil (Anexate), has been demonstrated as a benzodiazepine antagonist in volunteers [7, 8] and it has been shown to be tolerated well in oral doses up to 200 mg [9]. There have been investigations into the efficacy of flumazenil in antagonizing benzodiazepine sedation after minor surgical procedures [10, 11] and after endoscopy [12, 13]. Patients given flumazenil have been compared with those given placebo and appeared less sedated [11, 13], and performed better in psychometric tasks [12].

The aims of this study were to examine psychomotor function and subjective assessment of recovery after antagonism of benzodiazepine sedation in day-case gastroscopy patients, and to assess the ease of determining the correct dose of active antagonist.

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## PATIENTS AND METHODS

The study was approved by the Divisional Ethics Committee. After giving informed consent, patients of ASA classes I and II, aged 18–75 yr and scheduled to undergo day-case gastroscopy were allocated randomly to receive either diazepam or midazolam for sedation and flumazenil or placebo as antagonizing agent. The allocation of the sedative was determined with a code sheet available to the anaesthetist, but both the patient and the psychologist who assessed recovery were blind to the identity of the sedative. The allocation of the antagonist was double-blind, using coded ampoules packaged by Roche; the code was not broken until after completion of the data collection. These ampoules contained 20 ml of one of three substances: flumazenil 10 μg $\text{ml}^{-1}$, flumazenil 5 μg $\text{ml}^{-1}$ or placebo. The sedative and antagonist were administered by one of four anaesthetists, and the assessment was undertaken by a psychologist (L.D.S.). Patients receiving cimetidine, which is believed to affect the metabolism of benzodiazepines [14], those taking benzodiazepines and those for whom disability precluded completion of the test battery were excluded from the study.

On arrival in the day unit, each patient was instructed in and allowed a practice attempt with the psychometric tests, after which baseline measurements were taken.

Patients were premedicated with atropine 0.6 mg i.m. 30 min before the procedure unless the drug was contraindicated. A suitable vein was cannulated and either diazepam emulsion 0.2 mg $\text{kg}^{-1}$ or midazolam 0.1 mg $\text{kg}^{-1}$ administered i.v. The oropharynx was sprayed with 10% lignocaine solution from a metered-dose aerosol, and the endoscopic procedure was commenced. When required, increments of benzodiazepine were administered sufficient to allow the patient to tolerate the procedure.

At the end of the procedure, the patient was transferred to a recovery area, where the antagonizing agent was administered. An initial injection was given of 2 ml for the first 24 patients and 6 ml for the remaining 96, followed by increments of 2 ml every 2 min until it appeared to the anaesthetist that the sedation was antagonized completely or until a total of 20 ml of solution had been administered.

Both directly before and immediately after the administration of the antagonist, each patient was assessed on a five-point scale: awake, awake but drowsy, easily rousable, rousable with difficulty and unrousable. Orientation in time and space were assessed by direct questioning and co-operation was assessed by requesting the patient to raise the left thumb.

Psychomotor performance was assessed at 20, 90 and 180 min after administration of the antagonist and the patient was given a questionnaire to complete at home the next morning.

### *Psychometric tests*

*Critical flicker fusion threshold (CFFT).* The standard hand-held Leeds psychomotor tester was used to determine the threshold at which a flickering light was perceived as being constant and, conversely, when a flicker could be detected in a constant light. Ambient light, image size, illumination and viewing distance remained constant throughout the testing sessions. This test is thought to be an objective measure of cortical arousal. The score used was the mean of three ascending and three descending trials and was expressed in Hz [15].

*Aiming task.* This required the patient to draw dots in the centre of as many of a series of circles as possible in 60 s [16]. Two scores were derived from this: the total completed and the number of errors.

*Paired associatives task (PAT).* This tested short-term semantic recognition (after the Wechsler Memory Scale [17]). The patient was read a list of 10 pairs of words: in six pairs the two words had an obvious connection, in the remaining four there was no association. Recognition was tested immediately by reading the first word of each pair followed by four other words, one of which had been in the original pair. The score was derived from the number correctly identified, with the non-associated words scoring double (maximum 14).

*Prospective memory cards (PMC).* At the pre-drug session, the patient was given a series of cards and asked to return one to the psychologist at each subsequent visit. It was explained that after the end of that first session no further reminders of this task would be given. This task was designed to assess the patient's ability to store and act upon pre-drug instructions.

Apart from these measures, each patient was also questioned closely at each post-gastroscopy session for recall of the procedure, of the interaction with the endoscopist and of the events in the recovery room with the anaesthetist.

### *Subjective measures*

A set of visual analogue scales (VAS) was used for patients to record how they felt on the following dimensions: anxious, sleepy, headache, confused, blurred vision, weak, light-headed, hot, shivery, coughing, nauseous and vomiting—the last five being distractors [18]. The first measure was taken at the preoperative session which not only provided a baseline for this test, but also enabled the VAS to be explained to patients whilst they were still alert and responsive before being impaired by the drug.

### *Statistics*

For each of the groups each post-drug session was compared with baseline to assess impairment using a paired *t* test for the normally-distributed data (CFFT and aiming total) and a Wilcoxon test for the aiming errors (PAT and VAS). To examine between-group comparisons, an ANOVA with baseline as covariance was used on the CFFT and aiming totals and a Mann–Whitney using the difference between pre- and post-drug session on the non-normally-distributed data. Chi-square was used for the categorical data.

## RESULTS

Data were collected from 120 patients. The six drug groups were comparable for weight, age and sex, and for quantity of sedative received (table I). A smaller volume of flumazenil than placebo was administered, as expected considering the double-blind administration procedure used. There was no correlation between the dose of diazepam or midazolam and that of flumazenil ($P = 0.21$ and $P = 0.34$, respectively), and there was no significant difference in the amount of sedative or the amount of antagonist given by the four anaesthetists ($P = 0.071$ and $P = 0.61$, respectively). A greater mean quantity of flumazenil was given to those who received the full-strength than to those who received the half-strength solution. However, the ranges of doses administered were not discrete. For patients given either of the two sedatives followed by the half-strength solution, the range of dose of flumazenil was 0.1–1.0 mg (the maximum range). For those who had received diazepam, the range of full-strength solution was 0.2–1.8 mg and for those given midazolam it was 0.2–2 mg (also the maximum range). Therefore, although the analyses of the clinical data refer to three antagonist groups (those given flumazenil full strength, half strength or placebo) the psychometric data use only two groups: those given placebo and those given the active antagonist.

The pattern of impairment and recovery after diazepam differed from that after midazolam and therefore the results are presented separately for the two sedatives.

### *Diazepam*

*Clinical assessment of recovery.* More patients in all three groups appeared fully awake after administration of the antagonist (table II). The percentage of each group who scored maximum marks for co-operation and orientation was similar both before and after the antagonist. A few patients in each group affirmed before receiving the antagonist that they could recall swallowing the gastroscope, but after the agent they denied this recall.

Two patients who were given placebo and one given flumazenil were unable to complete the 20-min post-drug session; at 90 min one from each group was unable to do so.

*Psychometric results.* CFFT was significantly lower for all three post-drug test points, indicating a lessening of cortical arousal for both the flumazenil and placebo groups, and there was no significant effect of the antagonist. In the aiming test, the total completed by the placebo groups was less after the sedative, but this was not significant ($P > 0.05$). There was a significant improvement in the flumazenil group compared with baseline in their totals at 90 and 180 min, and at 90 min there was a significant effect of the antagonist ($P < 0.01$). The lack of improvement in the placebo group could be interpreted as a form of impairment. In both groups, there was a significant increase in the number of errors at all three test sessions. By the final session, the error score of the placebo group was beginning to decrease, whereas for the flumazenil group at this point it was still increasing. In the results from the paired associatives test, both groups also showed a significant decrement in short-term verbal recognition at each test point. The number of patients who failed to return the prospective memory cards was similar in each group (table III).

TABLE I. *Patient characteristics (mean range))*

| | Diazepam group | | | Midazolam group | | |
|---|---|---|---|---|---|---|
| | Flumazenil 0.1 mg $cl^{-1}$ ($n = 20$) | Flumazenil 0.05 mg $cl^{-1}$ ($n = 20$) | Placebo ($n = 20$) | Flumazenil 0.1 mg $cl^{-1}$ ($n = 20$) | Flumazenil 0.05 mg $cl^{-1}$ ($n = 20$) | Placebo ($n = 20$) |
| Sex (M/F) | 10/10 | 10/10 | 9/11 | 10/10 | 12/8 | 14/6 |
| Age (yr) | 48.4 | 46.9 | 47.5 | 46.1 | 49.0 | 45.8 |
| | (21–74) | (19–63) | (18–65) | (25–70) | (20–73) | (19–68) |
| Weight (kg) | 73.9 | 66.3 | 66.6 | 65.0 | 65.2 | 67.0 |
| | (53–108) | (44–93) | (46–86) | (46–83) | (48–102) | (49–79) |
| Dose of sedative | | | | | | |
| (mg) | 14.4 | 14.7 | 11.8 | 8.4 | 6.8 | 7.3 |
| | (7.5–30) | (7.5–20) | (6–16) | (5–15) | (5–10) | (5–10) |
| (mg $kg^{-1}$) | 0.20 | 0.23 | 0.18 | 0.13 | 0.10 | 0.11 |
| | (0.1–0.4) | (0.1–0.3) | (0.1–0.3) | (0.1–0.2) | (0.1–0.2) | (0.1–0.2) |
| Dose of antagonist | | | | | | |
| (ml) | 8.1 | 10.0 | 11.68 | 8.15 | 7.2 | 17.05 |
| | (2–18) | (2–20) | (2–20) | (2–20) | (2–20) | (2–20) |
| Flumazenil content | 0.81 | 0.50 | — | 0.82 | 0.36 | — |
| (mg) | (0.2–1.8) | (0.1–1.0) | — | (0.2–2.0) | (0.1–1.0) | — |

TABLE II. *Percentage of patients with optimal score on clinical signs of recovery*

| | Diazepam group | | | Midazolam group | | |
|---|---|---|---|---|---|---|
| | Flumazenil 0.1 mg $cl^{-1}$ ($n = 20$) | Flumazenil 0.05 mg $cl^{-1}$ ($n = 20$) | Placebo ($n = 20$) | Flumazenil 0.1 mg $cl^{-1}$ ($n = 20$) | Flumazenil 0.05 mg $cl^{-1}$ ($n = 20$) | Placebo ($n = 20$) |
| Before antagonist | | | | | | |
| Fully awake (%) | 47 | 35 | 35 | 27 | 25 | 20 |
| Co-operative (%) | 100 | 77 | 87 | 67 | 50 | 53 |
| Orientated in space (%) | 88 | 100 | 100 | 93 | 79 | 80 |
| Orientated in time (%) | 100 | 82 | 100 | 53 | 67 | 67 |
| Recalls procedure (%) | 86 | 80 | 93 | 55 | 45 | 36 |
| After antagonist | | | | | | |
| Fully awake (%) | 100 | 95 | 94 | 63 | 75 | 15 |
| Co-operative (%) | 95 | 95 | 94 | 94 | 90 | 80 |
| Orientated in space (%) | 95 | 95 | 100 | 100 | 90 | 80 |
| Orientated in time (%) | 95 | 85 | 94 | 100 | 90 | 50 |
| Recalls procedure (%) | 79 | 72 | 71 | 6 | 28 | 28 |

*Recall of events.* The proportion of both groups who could recall the events in theatre was similar at all three test points, but a smaller percentage of patients given placebo could recall events in recovery; this difference was not significant. A prompt at the final session enabled nearly all those in the flumazenil group who had not recalled events up to that point to do so (table IV).

*Subjective assessment.* At 20 min, the placebo group recorded confusion ($P < 0.05$), blurred vision ($P < 0.05$) and light-headedness ($P < 0.01$); the flumazenil group reported sleepiness ($P < 0.01$), headache ($P < 0.01$), weakness ($P < 0.05$) and light-headedness ($P < 0.001$). At 90 min the placebo group recorded only light-headedness ($P < 0.05$), whilst the flumazenil group reported headache ($P < 0.01$) and light-headedness ($P < 0.01$). By 180 min the only symptom reported was headache, by the flumazenil group ($P < 0.05$). During the rest of the day the placebo group reported experiencing sleepiness ($P < 0.05$) and the flumazenil group sleepiness ($P < 0.01$) and headache ($P < 0.05$). By the next morning, the placebo group indicated no symptoms, whilst the flumazenil group reported experiencing significantly less confusion and blurred vision than at baseline ($P < 0.05$) (table

Table III. *Psychometric results (mean* (SD)). *CFFT = Critical flicker fusion threshold; PAT = paired associatives task; PMC = prospective memory cards. Comparison of placebo with flumazenil groups:* ††$P < 0.01$; *within groups comparison with baseline:* *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

| | Diazepam group | | | Midazolam group | | |
|---|---|---|---|---|---|---|
| | Placebo (*n* = 20) | | Flumazenil (*n* = 40) | Placebo (*n* = 20) | | Flumazenil (*n* = 20) |
| CFFT | | | | | | |
| Baseline | 25.6 (3.1) | | 24.8 (3.0) | 25.7 (3.9) | | 25.5 (3.0) |
| After antagonism | | | | | | |
| 20 min | 23.7 (3.0)** | | 23.0 (2.8)*** | 21.3 (3.4)*** | | 22.7 (2.5)*** |
| 90 min | 23.7 (3.1)** | | 24.0 (3.3)* | 23.7 (3.5)** | | 22.8 (2.1)*** |
| 180 min | 23.9 (3.1)*** | | 23.7 (3.3)** | 24.5 (4.3)* | | 23.7 (2.9)*** |
| Aiming total | | | | | | |
| Baseline | 89.4 (16.9) | | 90.1 (19.0) | 83.5 (24.2) | | 90.8 (23.3) |
| After antagonism | | | | | | |
| 20 min | 81.3 (20.0) | | 90.7 (21.7) | 64.5 (17.0)* | †† | 85.0 (23.4)* |
| 90 min | 86.6 (17.0) | †† | 96.3 (20.3)** | 83.3 (19.7) | | 96.2 (25.2) |
| 180 min | 93.5 (15.4) | | 100.2 (22.0)*** | 85.8 (23.5) | | 98.4 (25.9)* |
| Errors | | | | | | |
| Baseline | 2.8 (2.9) | | 5.3 (5.3) | 5.8 (6.9) | | 6.5 (7.2) |
| After antagonism | | | | | | |
| 20 min | 10.2 (8.0)*** | | 14.4 (15.8)*** | 25.7 (18.9)** | | 25.5 (27.6)*** |
| 90 min | 10.0 (10.2)*** | | 16.3 (18.9)*** | 21.1 (17.8)** | | 24.2 (30.7)*** |
| 180 min | 9.2 (7.0)*** | | 19.8 (22.9)*** | 17.8 (17.9)** | | 20.9 (27.2)*** |
| PAT | | | | | | |
| Baseline | 11.7 (2.7) | | 11.7 (3.1) | 11.2 (2.4) | | 11.3 (2.8) |
| After antagonism | | | | | | |
| 20 min | 9.7 (3.5)** | | 10.3 (3.0)*** | 5.9 (4.1)** | †† | 8.5 (3.1)*** |
| 90 min | 10.0 (3.9)* | | 10.0 (3.5)*** | 7.5 (3.5)*** | | 9.0 (3.1)*** |
| 180 min | 10.1 (3.1)* | | 10.4 (3.4)* | 10.4 (3.8) | | 10.6 (2.8) |
| PMC, forgotten (%) | | | | | | |
| After antagonism | | | | | | |
| 20 min | 6 | | 11 | 12 | | 11 |
| 90 min | 26 | | 6 | 18 | | 11 |
| 180 min | 6 | | 11 | 11 | | 3 |

TABLE IV. *Percentage of patients recalling events.* ***$P < 0.001$ *(chi-square)*

| | Diazepam group | | Midazolam group | | |
|---|---|---|---|---|---|
| Event recalled | Placebo (*n* = 20) | Flumazenil (*n* = 40) | Placebo (*n* = 20) | | Flumazenil (*n* = 40) |
| Swallowing tube | | | | | |
| After antagonism | | | | | |
| 20 min | 72 | 68 | 19 | | 13 |
| 90 min | 75 | 67 | 18 | | 37 |
| 180 min | 69 | 60 | 11 | | 6 |
| Speech with endoscopist | | | | | |
| After antagonism | | | | | |
| 20 min | 69 | 72 | 18 | | 25 |
| 90 min | 70 | 73 | 14 | | 21 |
| 180 min | 60 | 69 | 13 | | 19 |
| Recovery room questions | | | | | |
| After antagonism | | | | | |
| 20 min | 39 | 65 | 0 | *** | 57 |
| 90 min | 47 | 64 | 0 | *** | 56 |
| 180 min | 53 | 53 | 0 | *** | 52 |
| Only with prompting | 24 | 44 | 5 | *** | 24 |

TABLE V. *Subjective assessment (VAS). Within groups comparison with baseline*: *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$

| | Diazepam group | | Midazolam group | |
|---|---|---|---|---|
| | Placebo | Flumazenil | Placebo | Flumazenil |
| Baseline | | | | |
| Sleepiness | 28.3 (21.2) | 26.6 (25.4) | 34.2 (27.5) | 29.6 (22.8) |
| Headache | 5.3 (4.7) | 11.2 (16.5) | 10.1 (11.7) | 13.6 (22.3) |
| Confusion | 17.4 (20.8) | 23.0 (25.7) | 21.3 (24.4) | 22.7 (27.0) |
| Blurred vision | 8.8 (10.8) | 18.2 (26.3) | 20.1 (27.6) | 14.4 (22.1) |
| Weakness | 27.3 (26.0) | 25.3 (24.6) | 38.5 (31.9) | 27.4 (24.2) |
| Light-headedness | 10.8 (15.3) | 17.3 (22.7) | 13.9 (20.6) | 19.9 (25.7) |
| Antagonism +20 min | | | | |
| Sleepiness | 47.8 (33.5) | 43.6 (27.2)** | 68.1 (22.6)* | 53.2 (30.7)*** |
| Headache | 13.6 (22.4) | 20.4 (27.0)** | 11.1 (14.7) | 23.7 (27.7)* |
| Confusion | 36.0 (28.9)* | 27.0 (24.8) | 47.3 (22.8)* | 34.0 (24.0)** |
| Blurred vision | 26.7 (33.0)* | 27.5 (31.3) | 21.1 (21.6) | 25.2 (26.4)* |
| Weakness | 38.3 (27.4) | 38.3 (26.4)* | 46.7 (27.7) | 37.9 (26.4) |
| Light-headedness | 45.1 (34.9)** | 44.7 (32.1)*** | 57.2 (29.7)* | 52.5 (33.8)*** |
| Antagonism +90 min | | | | |
| Sleepiness | 39.1 (32.9) | 32.2 (25.7) | 46.7 (28.7) | 41.0 (29.4) |
| Headache | 15.8 (25.8) | 21.0 (26.1)** | 19.2 (21.3)* | 18.2 (24.4) |
| Confusion | 19.5 (22.3) | 21.7 (21.8) | 30.2 (19.6) | 22.1 (21.0) |
| Blurred vision | 15.2 (20.0) | 16.5 (23.5) | 22.9 (25.0) | 16.5 (20.5) |
| Weakness | 31.6 (29.0) | 27.2 (22.5) | 39.1 (25.6) | 28.0 (21.9) |
| Light-headedness | 25.0 (31.4)* | 31.7 (29.8)** | 43.3 (32.0)** | 40.0 (33.3)** |
| Antagonism +180 min | | | | |
| Sleepiness | 24.3 (26.6) | 29.9 (29.6) | 34.6 (28.2) | 26.0 (22.7) |
| Headache | 15.6 (21.5) | 21.7 (29.4)* | 25.6 (30.6) | 17.5 (24.4) |
| Confusion | 14.1 (15.2) | 21.1 (23.1) | 13.8 (12.6) | 20.5 (20.5) |
| Blurred vision | 11.2 (16.4) | 13.3 (23.1) | 12.8 (13.3) | 13.9 (16.1) |
| Weakness | 24.9 (24.6) | 21.6 (19.9) | 30.8 (25.4) | 22.3 (19.6) |
| Light-headedness | 25.6 (32.9) | 27.1 (30.6) | 22.8 (25.5) | 28.4 (30.3) |
| Afternoon/evening | | | | |
| Sleepiness | 46.3 (26.1)* | 40.5 (25.7)** | 39.7 (33.1) | 38.7 (29.3) |
| Headache | 14.6 (20.1) | 23.3 (24.3)* | 19.6 (27.7) | 26.3 (29.0)* |
| Confusion | 18.3 (25.4) | 13.9 (19.7) | 18.1 (23.6) | 17.3 (24.6) |
| Blurred vision | 8.4 (11.5) | 8.1 (14.1) | 9.0 (12.1)* | 10.8 (18.7) |
| Weakness | 43.3 (30.0) | 31.8 (23.0) | 33.6 (29.0) | 35.4 (30.7) |
| Light-headedness | 21.9 (26.4) | 19.9 (19.7) | 19.2 (24.9) | 25.6 (25.2) |
| Next morning | | | | |
| Sleepiness | 22.1 (27.7) | 19.0 (20.3) | 23.3 (22.0) | 23.5 (21.4) |
| Headache | 9.7 (17.5) | 11.4 (19.0) | 17.2 (29.0) | 18.2 (25.2) |
| Confusion | 15.4 (23.0) | 8.9 (10.6)** | 15.7 (23.8) | 19.2 (26.2) |
| Blurred vision | 7.0 (11.3) | 9.1 (15.4)* | 6.2 (5.8)* | 7.0 (9.6) |
| Weakness | 19.7 (24.7) | 24.3 (20.2) | 25.3 (30.0) | 22.8 (22.9) |
| Light-headedness | 14.4 (19.5) | 14.5 (22.2) | 14.4 (23.3) | 16.9 (25.6) |

V). Because of the multiplicity of tests, it is possible that some of the significance levels quoted above and in table V are spurious. The very conservative Bonferroni correction could be applied and this would mean that a $P$ value of 0.0042 would be required before a result may be termed significant. In this case, the placebo group reported only an increase in light-headedness at 20 min, whereas the flumazenil group recorded headache and light-headedness at both 20 and 90 min.

### *Midazolam*

*Clinical assessment of recovery.* After the administration of the antidote, there was a large increase in the number of patients in both flumazenil groups, who appeared fully awake and who could orientate themselves in time. In all three groups, more became fully co-operative. A few patients in each group affirmed before receiving the antagonist that they could recall swallowing the gastroscope, but after the agent they denied this recall (table II). Six patients who were given placebo and one given flumazenil were unable to complete the 20-min post-drug session; at 90 min two in the placebo and three in the flumazenil group were unable to do so.

*Psychometric results.* As with the diazepam group, CFFT was significantly lower for all three post-drug test points, indicating a lessening of cortical arousal for both the flumazenil and placebo groups, and there was no significant effect of the antagonist. In the aiming test, the total completed was significantly lower after the sedative for both groups ($P < 0.05$), and there was also a significant effect of the antagonist ($P < 0.05$). The flumazenil group showed a significant improvement compared with baseline in the total at 180 min, which was not found in the placebo group. Both groups showed a significant increase in the number of errors of all three test sessions, which was beginning to decrease by 180 min. In the results from the paired associatives test, both groups also showed a significant decrement in short-term verbal recognition at 20 and 90 min, but this had gone by 180 min. The number of patients who failed to return the prospective memory cards was similar in each group (table III).

*Recall of events.* Very few patients in either group could recall events in theatre at any stage. However, of the flumazenil group, more than 50% could recall events in recovery without being prompted, compared with the placebo group who were unable to recall the recovery room ($P < 0.001$) (table IV).

*Subjective assessment.* At 20 min the placebo group felt sleepy ($P < 0.05$), confused ($P < 0.05$) and light-headed ($P < 0.05$), and the flumazenil group recorded sleepiness ($P < 0.001$), headache ($P < 0.05$), confusion ($P < 0.01$), blurred vision ($P < 0.05$) and light-headedness ($P < 0.001$). At 90 min the placebo group reported light-headedness ($P < 0.01$) and headache ($P < 0.05$), while the flumazenil group recorded only light-headedness ($P < 0.01$). By 180 min both groups had no symptoms, but the flumazenil group reported headache during the rest of the day. The placebo group recorded a significant reduction in blurred vision later that day and the following morning compared with baseline ($P < 0.05$) (table V). Again, because of the multiplicity of tests, it is possible that some of these significance levels are spurious. Application here of the Bonferroni correction would mean that the placebo group reported only an increase in light-headedness at 90 min, whereas the flumazenil group recorded sleepiness at 20 min and light-headedness at both 20 and 90 min.

## DISCUSSION

In this study the antagonizing agent was titrated until sedation appeared to be antagonized. It would be reasonable to expect, therefore, that a smaller volume of the full-strength than of the half-strength flumazenil would be given and that the full 20 ml of placebo would be given. However, this was not the case, which suggests that judging when antagonism has occurred is not a simple issue. There was no correlation between the quantities of sedative and of antagonist, and for those patients sedated with midazolam, a smaller volume of the half-strength than of the full-strength solution was given. The variability of response to benzodiazepines has been noted previously [6], from which it could be expected that antagonism of that sedation would be equally variable. Amongst the patients sedated with diazepam, the dose of placebo was only slightly greater than the dose of half-strength flumazenil. This accords with the data on the clinical signs of recovery. Amongst both groups of patients given placebo, there was some evidence of arousal after administration of the antagonist, active or inert. This suggests that the events in the recovery room themselves had a limited effect on waking the patients. It is possible to conclude that it is not easy to determine the optimal dose by clinical judgement.

With both sedatives, a few patients appeared to recall swallowing the gastroscope before the antagonist, but not afterwards. Whilst this could indicate a loss or corruption of the memory trace, it is more likely to reflect a change in the arousal levels of the patients. As this question required only "yes" or "no" in answer, in the earlier, more sedated state, patients may have been prepared to acquiesce without fully comprehending. Support for this can be seen in the data for the patients given diazepam amongst whom the most marked effect was found in the placebo group.

After placebo, fewer could recall the events of the recovery room than recalled events in theatre, which is likely to be a function of the salience of these events to the patients. The pattern of patients' recall of events suggests that flumazenil may reduce further anterograde amnesia; this was most pronounced after midazolam, as would be expected as it has been shown to be a more effective amnesiac [6].

The results of the psychometric tests showed that all patients were still impaired at the time of discharge from hospital. This is anticipated routinely in the Day Unit and patients are cautioned accordingly. The results of the CFFT and PAT seem to suggest a marginal trend towards smaller deficits in these higher cognitive functions in the patients given flumazenil, although there was no significant effect of the antagonist. In the cruder aiming task, there was a significant effect, which occurred earlier after midazolam than after diazepam, as would be expected given the shorter, more pronounced effect of midazolam sedation. This suggests that flumazenil was antagonizing most effectively the more basic function of motor co-ordination. Resedation has been demonstrated after flumazenil [8], but there was no evidence of this in psychometric results from this study. The relatively high proportion of patients given midazolam followed by placebo compared with those given flumazenil who were too sedated to complete the first test session demonstrates that flumazenil had antagonized the hypnotic effect of the sedative. This accords with the findings of two earlier studies [10, 19], and confirms the conclusion of one author that flumazenil may fail to antagonize completely the benzodiazepine effects on complex intellectual function, whilst antagonism of the hypnotic effect may be more complete [19]. The incidence of significant side effects reported by patients after flumazenil was greater than after placebo, which tends to support the hypothesis that the antagonist was keeping awake patients who might have benefited from sleeping. These data provide evidence for a more complex analysis of sedation than is routinely supposed. Flumazenil may appear to the onlooker to antagonize the obvious effects of sedation, as it seems to wake patients, but this antagonism would appear to affect differentially the hierarchy of cognitive functions, leaving the higher functions impaired. This complex model of sedation requires further investigation.

In conclusion, the routine use of flumazenil for day-case gastroscopy patients cannot be recommended. If patients appear more awake, they are likely to be discharged earlier whilst still experiencing undetected residual cognitive impairment.

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# EFFECT OF I.V. MIDAZOLAM ON THE VENTILATORY RESPONSE TO SUSTAINED HYPOXIA IN MAN

A. DAHAN AND D. S. WARD

**SUMMARY**

*The ventilatory response to isocapnic, sustained hypoxia is characterized by initial hyperventilation followed by ventilatory decline. The ventilatory response to isocapnic sustained hypoxia during i.v. administration of midazolam was assessed in five healthy subjects. Compared with control experiments, the hyperventilatory effect of hypoxia was not decreased following administration of midazolam. The hypoxic ventilatory change was significantly greater with midazolam because of a decrease in tidal volume.*

**KEY WORDS**

*Hypnotics midazolam. Ventilation · hypoxic response*

The sudden imposition of isocapnic hypoxia results in a rapid increase in ventilation in awake man. However, this initial period of hyperventilation is usually not sustained longer than 5 min and is followed by a slow decrease in ventilation ($\dot{V}$E) that reaches a new steady state $\dot{V}$E after 15–20 min [1, 2]. The initial increase in $\dot{V}$E is driven by peripheral chemoreceptors, while the subsequent decrease has a central origin [3]. It has been suggested that the release or accumulation, or both, of inhibitory neuromodulators such as γ-aminobutyric acid (GABA) and adenosine in the brainstem during exposure to moderate hypoxia is the main cause of the hypoxic ventilatory depression [4–6].

Until recently, only the effects of drugs on the acute hyperventilatory response have been studied. The effects on prolonged hypoxia have been investigated only rarely. Midazolam, in common with other benzodiazepines, potentiates the effects of GABA [7] and thus could potentially change the ventilatory response to sustained hypoxia. We therefore investigated the effect of midazolam on the development of hypoxic ventilatory change in man.

## SUBJECTS AND METHODS

We studied five healthy male subjects (mean age 24 yr, mean body weight 77 kg) with no history of cardiovascular or respiratory disease. Informed consent was obtained and the local subjects protection committee approved the study. All subjects were naïve to respiratory physiology and unaware of the purpose of this study, but had participated before in other respiratory studies. They were asked to refrain from stimulants for at least 12 h before the experiment.

The subjects breathed via a mouthpiece and wore a noseclip. The oxygen and carbon dioxide concentrations and the gas flow of the inspired and expired gas were measured with a mass spectrometer (Perkin Elmer 1100 MGA, U.S.A.) and a turbine flow meter (VMM-1, Sensor Medics, U.S.A.), respectively. The ECG was monitored and a pulse oximeter (Ohmeda Biox 3700, U.S.A.) used to measure arterial oxygen saturation via an ear probe. The tidal volume, ventilatory frequency, $\dot{V}$E and end-tidal partial pressures of carbon dioxide ($P\text{E}'_{CO_2}$) and oxygen ($P\text{E}'_{O_2}$) were calculated by a computer and stored on a breath-to-breath basis using the TIDAL software package [8].

The mouthpiece and flowmeter were connected to a gas mixing chamber. The gas flow to the chamber was controlled by two servo valves, by which the flows of oxygen and carbon dioxide could be set individually as desired. The main flow of gas in the mixing chamber consisted of nitrogen, room air, or both. The computer provided control signals to the servo valves, so

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TABLE I. *Ventilatory response to hypoxia (mean* (SD)). *A = 3-min period before hypoxia; B = 3-min period following the first 2 min of hypoxia; C = 12–15 min of hypoxia.* $P \leqslant 0.05$ *compared with *period A or †period B*

| | Period A | Period B | Period C |
|---|---|---|---|
| $P\mathrm{E}'_{\mathrm{CO}_2}$ (kPa) | | | |
| Control | 6.16 (0.55) | 6.08 (0.54) | 6.11 (0.58) |
| Midazolam | 6.27 (0.39) | 6.23 (0.41) | 6.21 (0.42) |
| $P\mathrm{E}'_{\mathrm{O}_2}$ (kPa) | | | |
| Control | 14.52 (0.09) | 7.02 (0.06)* | 7.02 (0.03)* |
| Midazolam | 14.53 (0.05) | 6.93 (0.08)* | 7.03 (0.07)* |
| $\dot{V}\mathrm{E}$ (litre $\min^{-1}$) | | | |
| Control | 12.20 (5.21) | 21.49 (10.96)* | 19.19 (8.52)* |
| Midazolam | 8.45 (3.23) | 15.24 (6.34)* | 9.28 (3.57)† |
| Tidal volume (litre) | | | |
| Control | 0.96 (0.26) | 1.43 (0.44)* | 1.28 (0.42)* |
| Midazolam | 0.71 (0.23) | 1.01 (0.34)* | 0.77 (0.24)† |
| Ventilatory frequency (b.p.m.) | | | |
| Control | 13.93 (3.94) | 15.74 (3.97)* | 16.16 (2.67)* |
| Midazolam | 13.97 (0.76) | 16.55 (2.85) | 14.35 (1.90) |

that the composition of the inspiratory gas mixture could be adjusted to permit $P\mathrm{E}'_{\mathrm{CO}_2}$ and $P\mathrm{E}'_{\mathrm{O}_2}$ to follow a specific dynamic pattern in time.

After the subjects arrived at the laboratory, an i.v. infusion of normal saline 100 ml $\mathrm{h}^{-1}$ was started. Subsequently, the subjects rested for 30 min. Following this rest period, a control hypoxic experiment was performed. Subsequently, an infusion of midazolam 0.025 mg $\mathrm{kg}^{-1}$ was given over 10 min, followed by a continuous infusion of 1.0 mg/70 kg $\mathrm{h}^{-1}$. Thirty minutes after the start of the infusion, a second experiment was performed.

The experiments consisted of a 5-min period of steady state ventilation during which $P\mathrm{E}'_{\mathrm{O}_2}$ was held constant at 14.5 kPa, followed by a rapid decrease in $P\mathrm{E}'_{\mathrm{O}_2}$ to 7 kPa, which was maintained constant for 20 min. Each hypoxic episode was followed by inhalation of 100% oxygen for 7 min to eliminate residual effects of hypoxia [4]. During the control experiment, $P\mathrm{E}'_{\mathrm{CO}_2}$ was increased to slightly greater than resting value and kept *constant* at this value during both control and midazolam experiments ($P\mathrm{E}'_{\mathrm{CO}_2}$ 5.5–6.2 kPa between subjects), to anticipate the development of hypercapnia after infusion of midazolam and to maintain control of $P\mathrm{E}'_{\mathrm{CO}_2}$ even if $\dot{V}\mathrm{E}$ decreased to less than the normoxic value.

### *Data analysis*

For statistical comparisons, we calculated the mean of the breath-to-breath values of the 3-min period before hypoxia (period A), the 3-min period following the first 2 min of hypoxia (period B), and 12–15 min of the hypoxic period (period C). The prolonged hypoxia caused some subjects to become restless towards the end of the period, particularly during the control studies. As this occurred generally during the last 5 min, this period was excluded from analysis.

Data were subjected to two-way analysis of variance with *post-hoc* multiple comparisons with Newman–Keuls test and paired *t* test as appropriate using the SOLO (BMDP Inc.) computer package. $P \leqslant 0.05$ was taken as significant.

## RESULTS

All subjects became lightly sedated during the administration of midazolam, but remained easily rousable. None experienced any side effects and all had partial amnesia for the procedure.

The mean values of the variables for the periods A, B and C are shown in table I. During the control experiments, all but one subject showed the typical biphasic response after exposure to hypoxia. The mean initial increase in $\dot{V}\mathrm{E}$ of 9.3 litre $\min^{-1}$ was followed by a small decrease of 2.3 litre $\min^{-1}$. During the midazolam experiments, the mean ventilatory increase of 6.8 litre $\min^{-1}$ was followed by a decrease of 5.9 litre $\min^{-1}$, which resulted in an almost complete return of $\dot{V}\mathrm{E}$ to its initial value. In three subjects $\dot{V}\mathrm{E}$ was reduced in period C to less than that of period A. One subject showed no depression in his control experiment (fig. 1).

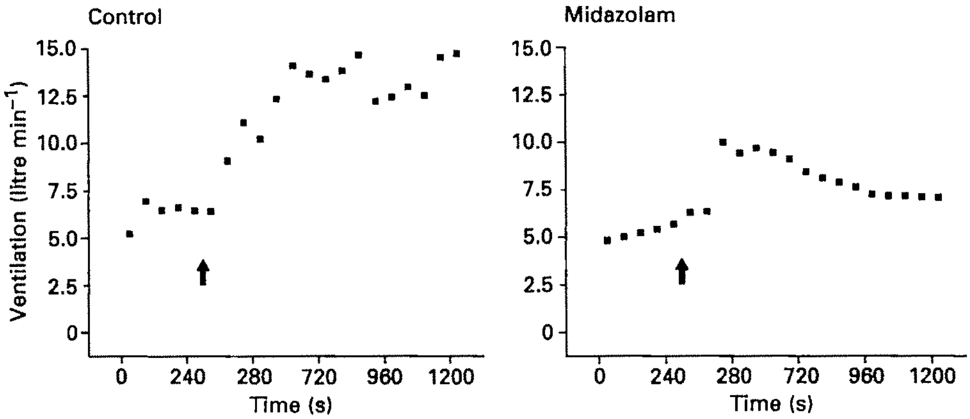

FIG. 1. Comparison of the ventilatory response to sustained isocapnic hypoxia in control and midazolam studies in a single subject. Each point represents a 60-s average of the breath-to-breath values. At time $t = 300$ s (arrows), hypoxia was induced.

TABLE II. *Mean* (SD) *changes in* $P\text{E}'_{CO_2}$ *and* $P\text{E}'_{O_2}$

| | (Period B − period A) | (Period C − period B) |
|---|---|---|
| $P\text{E}'_{CO_2}$ (kPa) | | |
| Control | −0.08 (0.12) | −0.03 (0.10) |
| Midazolam | −0.04 (0.05) | 0.02 (0.06) |
| $P\text{E}'_{O_2}$ (kPa) | | |
| Control | −7.50 (0.14) | −0.00 (0.05) |
| Midazolam | −7.60 (0.08) | −0.11 (0.12) |

The ventilatory increase from period A to period B did not differ significantly between control and midazolam experiments. However, the subsequent decrease from period B to period C, expressed as the ratio of ventilatory decrease to ventilatory increase, was greater in the midazolam group (96 % *vs* 18 %, $P = 0.01$). Visual inspection of the dynamics of the ventilatory response revealed that, in the four subjects who showed a decrease in the control experiments, the onset of decrease occurred at 4–6 min, while in the midazolam experiments it was at 1–3 min.

The control of $P\text{E}'_{CO_2}$ and $P\text{E}'_{O_2}$ in these experiments is important, because of the pronounced effect of their interaction on ventilation. The relatively large SD of $P\text{E}'_{CO_2}$ in the different periods in table I reflect *inter-subject variability* and not changes with time in one subject. This is shown in table II, where the average changes in $P\text{E}'_{CO_2}$ and $P\text{E}'_{O_2}$ for the three periods are given. $P\text{E}'_{CO_2}$ was slightly greater during the midazolam experiments than during the control experiments (approximately 0.1 kPa).

## DISCUSSION

*Hypoxic hyperventilation.* Although the acute ventilatory response to hypoxia was decreased with midazolam, it was not statistically significant in our group of subjects. This is at variance with the findings of Alexander and Gross [9], who found a reduced response after midazolam 0.1 mg kg$^{-1}$ i.v. administered over 5 min. The i.m. administration of diazepam 10 mg resulted also in a marked decrease in hyperventilatory response to hypoxia [10]. The discrepancy between these findings and ours may have been caused by several mechanisms: the small number of subjects in our study; the smaller dose used in our study, which caused less sedation; the slightly greater $P\text{E}'_{CO_2}$ in our midazolam experiments compared with the control experiments, which may have masked the decrease in the initial hyperventilation; and the use of a ramp hypoxic test, compared with the step hypoxic test we used. We found that the onset of ventilatory depression in the midazolam experiments was faster than that in the control group. It is therefore possible that, in contrast with their control group, by using a ramp decline in $P\text{E}'_{O_2}$, Alexander and Gross encountered the effects of hypoxic depression in their midazolam group.

*Hypoxic ventilatory decrease.* The magnitude of the hypoxic ventilatory decrease in our control group (18% of the initial increase) was smaller than the 64% decrease reported by Easton, Slykerman and Anthonisen [2]. However, it is similar to that found by Suzuki and colleagues [11], who reported that $\dot{V}\text{E}$ tended to decrease more clearly during sustained hypoxia in subjects with reduced hyperventilatory responses, whereas the change in $\dot{V}\text{E}$ was less apparent in subjects with increased hyperventilatory responses. Most of our subjects were in the latter group.

There are several possible mechanisms for the increase in the hypoxic ventilatory decrease observed in the midazolam experiments: an effect of the control experiment on the effects of midazolam; an effect of midazolam on the hypoxic peripheral chemoreceptor activation; an interaction of midazolam with the GABA–benzodiazepine receptor complex in the brain stem during hypoxia [7]; and an effect of midazolam on supra-pontine structures. Although none of the above can be excluded, the potentiation of the effect of GABA by midazolam during exposure to hypoxia is the most likely explanation for our observations. The further decrease in tidal volume with midazolam (table I) is typical for the GABA-mediated depression of $\dot{V}\text{E}$ [6]. Our study supports the hypothesis that the ventilatory decrease with hypoxia results, at least partly, from accumulation of the neuromodulator GABA.

The effect of midazolam on the hypoxic ventilatory decrease has some important clinical implications. Patients receiving sedative doses of midazolam who develop hypoxaemia may react with initial hyperventilation. Sustained hypoxaemia would result in decreased ventilatory drive and a further decrease in oxygenation. Midazolam obscures the usual clinical signs of hypoxaemia [9], and we suggest that the oxygenation of patients receiving sedative doses of midazolam should be monitored and the inspired oxygen concentration increased.

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# PHARMACOKINETIC STUDY OF EXTRADURAL AND INTRATHECAL SUFENTANIL ANAESTHESIA FOR MAJOR SURGERY

T. I. IONESCU, R. H. T. TAVERNE, P. L. HOUWELING, R. H. DROST, S. NUIJTEN AND J. VAN ROSSUM

## SUMMARY

*We have studied the plasma concentrations ($C_P$) and pharmacokinetics of sufentanil injected i.v. (IVS), intradurally (IS) or extradurally (ES) under general anaesthesia in 31 patients undergoing major abdominal surgery. Sufentanil appeared in plasma very rapidly and $C_P$max was also attained rapidly after both extradural and intrathecal injection. Apart from the first 2 min after injection, $C_P$ after ES and IVS were comparable until the end of the study. $C_P$ after ES was greater than after IS up to 0.25 h. $C_P$ after IS was significantly greater than that after ES at 1 h and 2.5 h, and was also greater than that after IVS at 3 h. At tracheal extubation there was no difference in $C_P$ between groups. Peak $C_P$ values were significantly different between ES and IS, but the times taken to reach $C_P$max were comparable. Plasma pharmacokinetics after ES and IS were similar. The plasma mean residence time and volume of distribution of sufentanil at steady state after ES and IS were significantly different in comparison with those after IVS.*

***KEY WORDS***

*Analgesics: sufentanil. Anaesthetic techniques: extradural, spinal. Pharmacokinetics: sufentanil*

Since the discovery of specific opioid receptors in the spinal cord and brain [1, 2], clinical evidence is accumulating that extradural and intrathecal administration of opioid analgesics produce excellent acute and chronic pain relief. The disposition of morphine, the oldest opioid agonist, has been studied frequently after extradural and intradural administration. Of all the new opioids introduced into clinical anesthesia during the past 25 years, sufentanil possesses the greatest potency and the greatest affinity for the specific opioid receptors. In recent years, sufentanil has been given by intrathecal and extradural routes for treatment of pain, but little is known of the pharmacokinetics of this mode of administration.

The purpose of the present study was to examine the plasma pharmacokinetics of sufentanil injected extradurally or intrathecally, under general anaesthesia, for major abdominal surgery.

## PATIENTS AND METHODS

The study was approved by the Hospital Ethics Committee. Informed consent was obtained from 31 patients, ASA physical status II, undergoing elective major abdominal surgery. Patients with liver, renal, heart or neurological disease were excluded from the study. No patient had been receiving opioids before the study. Premedication comprised midazolam 7.5–10 mg orally, 45–60 min before induction of anaesthesia.

Before operation, the patients were allocated randomly to three groups, to receive i.v. (IVS), extradural (ES) or intrathecal (IS) sufentanil anaesthesia. On arrival of the patient in the operating room, ECG lead V5, was displayed continuously. An i.v. cannula, a radial artery cannula, and an 18-gauge intrathecal catheter (introduced at L2–L3 and directed 3–4 cm cranially) were inserted in all patients. Depending on the clinical indication, in some patients a pul-

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TABLE I. *Patient characteristics (mean (range or* SD*)). AAIS = Abdominal aorto-iliac surgery; ATR = abdominal tumour removal*

| | I.v. | Extradural | Intrathecal |
|---|---|---|---|
| Sex (F/M) | 6/4 | 4/6 | 6/5 |
| Age (yr) | 58 (36–77) | 63 (45–72) | 56 (26–71) |
| Weight (kg) | 66 (8.8) | 75 (13.8) | 68 (16.7) |
| Height (cm) | 166 (6.7) | 171 (7.0) | 169 (8.5) |
| Surgical procedure | | | |
| AAIS | 2 | 5 | 7 |
| ATR | 8 | 5 | 4 |

monary artery catheter was introduced via the internal jugular vein, under local anesthesia for cardiovascular monitoring. The bladder was catheterized in all patients after tracheal intubation.

General anaesthesia was induced with midazolam 0.1–0.15 mg kg$^{-1}$, followed by vecuronium 0.1–0.15 mg kg$^{-1}$ and the lungs were ventilated with 50 % nitrous oxide in oxygen. Mechanical ventilation was assessed by measurement of end-expiratory concentration of carbon dioxide and repeated arterial blood-gas analysis. Anaesthesia was maintained with sufentanil, 50 % nitrous oxide in oxygen and increments of vecuronium. Sufentanil was injected as a bolus of 150 µg (3 ml) (Sufenta Forte) extradurally or intrathecally at T12–L1 or i.v. Patients receiving i.v. sufentanil served as a control group.

Blood loss was assessed by weighing surgical packs, swabs, etc., and measuring the blood suctioned from the surgical field into a single bottle. Blood loss was replaced by blood and fresh frozen plasma. All patients received 20 % albumin 100–200 ml and Ringer lactate 8–10 ml kg$^{-1}$ h, 2.5 % glucose–saline, or both throughout the operation. Blood and i.v. fluids were warmed before administration. An attempt was made to maintain body temperature greater than 35 °C using a warmed water mattress.

Arterial blood samples (5 ml) were obtained before, and at 2, 15, 30, 45, 60, 90, 120, 150 and 180 min after injection of sufentanil and at tracheal extubation. The blood was collected in tubes containing lithium heparin and centrifuged at 1500 *g* for 10 min. The supernatant plasma samples were frozen at $-40$ °C until required for analysis. Plasma concentration of sufentanil was measured by radioimmunoassay (RIA) using a commercial kit supplied by Janssen Pharmaceutica. The detection limit of the assay was 0.02 ng ml$^{-1}$ for plasma. The intra- and inter-assay coefficients of variation were on average 5.1 % and 6.2 %, respectively, over the range of 0.05–4 ng per test tube.

The statistical moments of areas (zero moment) and mean times (first moment) were used to analyse the sufentanil concentration curves in plasma [3]. The trapezoidal method was used to calculate the area under the concentration–time curve (AUC) and the area under the product of time and concentration–time curve (TAUC) for sufentanil, from zero to the time of tracheal extubation. Data were analysed statistically using the non-linear regression program PCNONLIN (SCI software). The pharmacokinetic parameters for plasma sufentanil, mean residence time (MRT), total plasma clearance ($Cl$) and the apparent volume of distribution at steady state ($Vd^{ss}$) were calculated from the moments of concentration–time curves as follows: MRT = TAUC/AUC; $Cl$ = Dose/AUC; $Vd^{ss}$ = MRT $\times Cl$.

The plasma maximal concentrations ($C_P$max) and the time taken to reach the maximal concentration ($tC_P$max) of sufentanil were calculated by curve fitting with the statistical analysis of the non-linear models program, PCNONLIN.

The fraction of sufentanil ($F$) that reached the central circulation after extradural and intrathecal administration at 1, 2, 3 h and tracheal extubation was calculated from the formula:

$$F = \text{AUC (ES or IS)} \times \text{dose (IVS)/AUC (IVS)} \times \text{dose (ES or IS)}$$

The duration of surgery, duration of analgesia, duration of tracheal intubation, blood loss and urine production up to the time of tracheal extubation were recorded. The duration of analgesia was defined as the time between the abdominal incision and the patient's first request for postoperative pain relief. Maintenance of normal arterial blood-gas values and end-ex-

TABLE II. *Mean* (SD) *plasma sufentanil concentrations after i.v., extradural and intrathecal administration for major abdominal surgery. TE = Tracheal extubation. Significant difference* ($P < 0.05$)*: *compared with the intrathecal group; †compared with the extradural group; §compared with the intrathecal group*

| | Plasma concn of sufentanil (ng ml$^{-1}$) | | |
|---|---|---|---|
| | I.v. | Extradural | Intrathecal |
| Time (h) | | | |
| 0.03 | 3.65 (2.06)*† | 0.71 (0.29)§ | 0.30 (0.22) |
| 0.25 | 1.14 (0.44)* | 0.72 (0.35)§ | 0.43 (0.21) |
| 0.5 | 0.60 (0.21) | 0.44 (0.27) | 0.43 (0.21) |
| 0.75 | 0.38 (0.12) | 0.30 (0.17) | 0.36 (0.09) |
| 1.0 | 0.28 (0.08) | 0.22 (0.11)§ | 0.31 (0.10) |
| 1.5 | 0.21 (0.08) | 0.16 (0.06) | 0.26 (0.10) |
| 2.0 | 0.16 (0.07) | 0.13 (0.07) | 0.22 (0.12) |
| 2.5 | 0.13 (0.04) | 0.11 (0.05)§ | 0.17 (0.07) |
| 3.0 | 0.10 (0.01)* | 0.12 (0.06) | 0.17 (0.07) |
| TE | 0.08 (0.02) | 0.10 (0.04) | 0.11 (0.03) |
| $C_P$max | | 0.82 (0.34)§ | 0.54 (0.21) |
| | Time of occurrence (h) | | |
| TE | 5.47 (1.41) | 5.66 (2.45) | 5.57 (1.16) |
| $tC_P$max | | 0.06 (0.03) | 0.11 (0.05) |

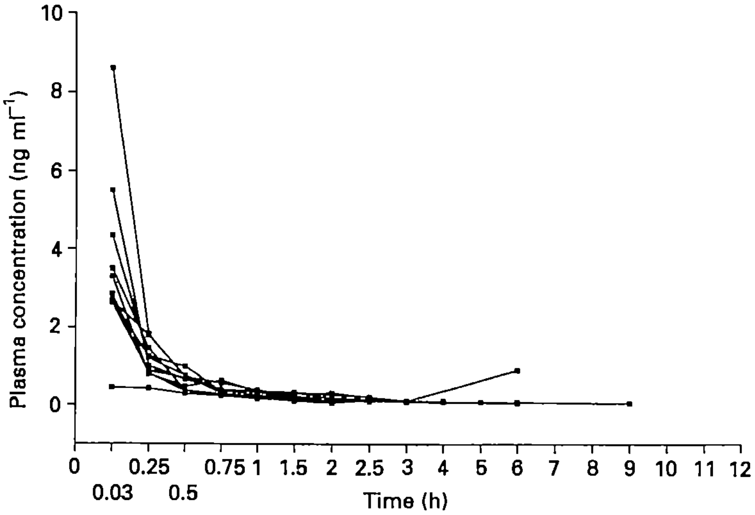

FIG. 1. Plot of the 10 sufentanil plasma concentration profiles after an i.v. bolus of 150 μg for major abdominal surgery.

piratory concentrations of carbon dioxide less than 5% (capnograph) for a period of at least 30 min during postoperative spontaneous ventilation were taken as the criteria for tracheal extubation.

*Statistics*

Where applicable, one- or two-way analysis of variance with the factors age, weight, height, plasma concentration and pharmacokinetic values were used. Significance was taken as $P < 0.05$.

## RESULTS

There were no significant differences in sex, age, weight or height between the groups (table I).

$C_P$ values after ES were comparable with those

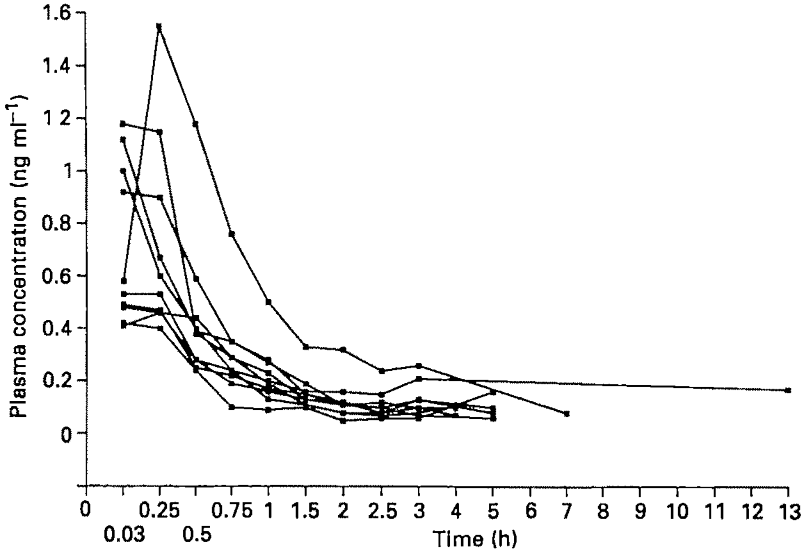

FIG. 2. Plot of the 10 sufentanil plasma concentration profiles after an extradural bolus of 150 µg for major abdominal surgery.

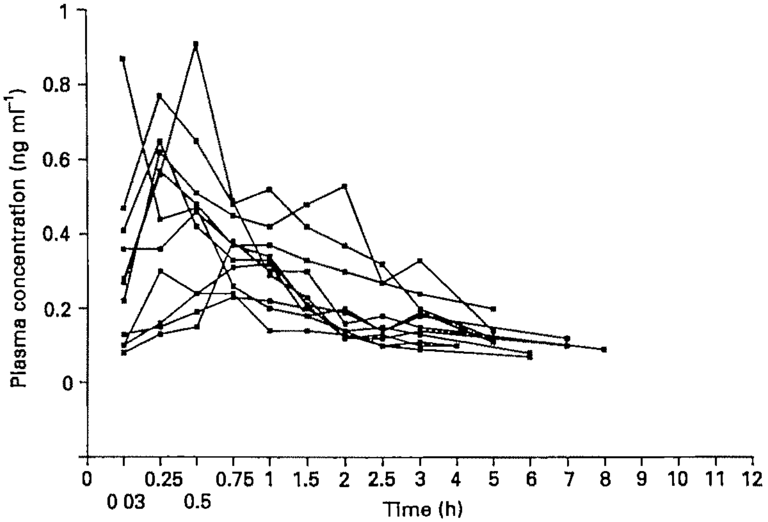

FIG. 3. Plot of the 11 sufentanil plasma concentration profiles after an intrathecal bolus of 150 µg for major abdominal surgery.

after IVS at all times except at 0.03 h (table II). $C_P$ values after IS were significantly less than those after IVS and ES at 0.03 h and 0.25 h and greater than $C_P$ after ES at 1 h and 2.5 h and that after IVS at 3 h. At tracheal extubation, $C_P$ were comparable between groups. $C_P$max of sufentanil were 0.82 (SD 0.34) ng ml$^{-1}$ at 0.06 (0.03) h ($tC_P$max) after ES and 0.54 (0.21) ng ml$^{-1}$ at 0.11 (0.05) h ($tC_P$max) after IS. The differences in $C_P$max between ES and IS were significant. The time taken to reach $C_P$max was comparable between groups ES and IS. Individual plots of plasma concentrations of sufentanil against time are shown in figures 1–3.

The fraction of sufentanil that reached the systemic circulation is shown in table III. After

TABLE III. *Mean* (SD) *fraction of sufentanil (F) that reached the central circulation after extradural and intrathecal injection for major abdominal surgery. TE = Tracheal extubation.* **Significant difference within group*

| Group | $\mathrm{AUC}_{0\text{–}1h}$ | | $\mathrm{AUC}_{0\text{–}2h}$ | | $\mathrm{AUC}_{0\text{–}3h}$ | | $\mathrm{AUC}_{0\text{–}TE}$ |
|---|---|---|---|---|---|---|---|
| I v. | 1.06 (0.41) | | 1.27 (0.43) | | 1.39 (0.43) | | 1.52 (0.48) |
| Extradural | 0.48 (0.21) | | 0.65 (0.28) | | 0.76 (0.33) | | 1.16 (0.69) |
| Fraction | 48.5 (26.1) | * | 53.2 (26.6) | * | 56.4 (26.3) | | 65.7 (27.2) |
| Intrathecal | 0.38 (0.14) | | 0.64 (0.21) | | 0.83 (0.27) | | 1.17 (0.30) |
| Fraction | 42.1 (17.4) | * | 56.8 (21.2) | * | 64.8 (23.3) | * | 76.9 (19.2) |

ES, it increased significantly up to 3 h, at which time it was comparable to that measured at tracheal extubation. Following IS, *F* increased significantly up to the time of tracheal extubation. Differences in *F* between the ES and IS groups were not significant at any time of measurement.

There was no significant difference in pharmacokinetic values between ES and IS groups. MRT and $Vd^{ss}$ after IVS were significantly less than those recorded after ES and IS (table IV).

The duration of surgery was 196 (80) min for group IVS, and 164 (49) min and 201 (72) min for the ES and IS groups, respectively. Duration of analgesia was 394 (70) min after IVS, 426 (144) min after ES and 379 (65) min after IS. Duration of tracheal intubation was 344 (62) min after IVS, 310 (40) min after ES and 335 (55) min after IS. Blood loss during surgery was 1268 (817) ml after IVS, 1188 (622) ml after ES and 1374 (732) ml after IS. Urine production during the study was 534 (274) ml after IVS, 324 (127) ml after ES and 430 (309) ml after IS. There were no significant differences between the groups.

## DISCUSSION

The initial systemic absorption of sufentanil after extradural injection was very rapid. Except at 0.03 h after injection of sufentanil, $C_P$ of IVS and ES were similar up to the end of the study. $C_P$max and the $tC_P$max for IVS and ES differed. $tC_P$max after ES was comparable to those reported by Sabbe and colleagues [4] with sufentanil 10, 50 or 100 µg extradurally in dogs, by de Sousa and Stiller [5] with sufentanil 200 µg extradurally in sheep, and by Klepper and colleagues [6] with sufentanil 50 µg extradurally in volunteers, but shorter than the $tC_P$max reported by Nordberg, Hedner and Mellstrand [7], who gave sufentanil 75 µg in saline 10 ml extradurally to surgical patients.

The transfer of sufentanil from the subarachnoid space to the systemic circulation also appeared to be rapid after IS. $C_P$ increased rapidly to $C_P$max. $C_P$max was significantly different between the IS and ES groups, but $tC_P$max values were comparable. After $C_P$max was reached, $C_P$ after IS seemed to remain somewhat greater than that after ES. The tendency to greater $C_P$ after IS than after ES would suggest that a larger amount of sufentanil is transferred to the central circulation from the CSF than from the extradural space during the study. However, this assumption is not supported by the fraction of sufentanil that reached the central circulation although, following ES, it increased up to 3 h, whilst following IS it continued to increase up to the time of tracheal extubation. This small difference may indicate that the entire dose of sufentanil injected intrathecally reached the central circulation earlier than that injected extradurally because sufentanil exists in free form in the protein-free CSF, whilst after extradural administration it remains bound to extradural fat. Its residence in the CSF is also not influenced by a decrease in CSF pH or temperature [8]. $C_P$ and *F* values in groups ES and IS were influenced strongly by the inter-individual variations in systemic absorption of sufentanil, caused by the following factors:

(a) CSF distribution of a hypobaric solution, such as Sufenta Forte, injected intrathecally is influenced by the position of the patient and the mechanical changes in abdominal and thoracic spaces during surgery and mechanical ventilation [9]. Thus absorption into the venous sinuses, via the arachnoid villi, may differ between patients.

(b) Drug absorbed through the extradural and spinal vessels flows into Batson's internal vertebral vein plexus and into the venous networks which surround the dura mater [10]. These vessels, which intercommunicate, drain into the basivertebral veins or venae cavae. Vasoconstriction of the lumbar vessels following aortic

TABLE IV. *Plasma pharmacokinetics of sufentanil after i.v., extradural and intrathecal injection. MRT and* $Vd^{ss}$ *values in the i.v. group are significantly less than those in the other two groups*

| Patient No. | AUC (ng ml$^{-1}$ h) | TAUC (ng ml$^{-1}$ h$^2$) | MRT (h) | *Cl* (litre h$^{-1}$) | $Vd^{ss}$ (litre) |
|---|---|---|---|---|---|
| Intravenous | | | | | |
| 1 | 1.80 | 1.76 | 0.98 | 83.33 | 81.48 |
| 2 | 1.60 | 1.45 | 0.91 | 93.75 | 84.96 |
| 3 | 1.29 | 0.74 | 0.57 | 116.28 | 66.70 |
| 4 | 1.47 | 1.45 | 0.99 | 102.04 | 100.65 |
| 5 | 1.29 | 1.52 | 1.18 | 116.28 | 137.01 |
| 6 | 1.55 | 2.11 | 1.36 | 96.77 | 131.74 |
| 7 | 1.36 | 0.91 | 0.67 | 110.29 | 73.80 |
| 8 | 0.54 | 0.57 | 1.06 | 277.78 | 293.21 |
| 9 | 1.75 | 1.69 | 0.97 | 85.71 | 82.78 |
| 10 | 2.57 | 1.99 | 0.77 | 58.37 | 45.19 |
| Mean | 1.52 | 1.42 | 0.94 | 114.06 | 109.75 |
| SD | 0.48 | 0.49 | 0.22 | 57.03 | 66.65 |
| Extradural | | | | | |
| 1 | 0.94 | 1.18 | 1.26 | 159.57 | 200.32 |
| 2 | 0.67 | 0.83 | 1.24 | 223.88 | 277.35 |
| 3 | 0.68 | 0.97 | 1.43 | 222.59 | 314.66 |
| 4 | 0.66 | 1.06 | 1.61 | 227.27 | 365.01 |
| 5 | 1.20 | 2.00 | 1.67 | 125.00 | 208.33 |
| 6 | 2.53 | 6.25 | 2.47 | 59.29 | 146.46 |
| 7 | 0.57 | 1.17 | 2.05 | 263.16 | 540.17 |
| 8 | 1.13 | 1.66 | 1.47 | 132.74 | 195.00 |
| 9 | 2.44 | 5.01 | 2.05 | 61.48 | 126.23 |
| 10 | 0.79 | 0.92 | 1.16 | 189.87 | 221.12 |
| Mean | 1.16 | 2.11 | 1.64 | 166.29 | 259.47 |
| SD | 0.69 | 1.82 | 0.41 | 67.26 | 116.43 |
| Intrathecal | | | | | |
| 1 | 1.38 | 2.87 | 2.08 | 108.70 | 226.05 |
| 2 | 1.64 | 2.78 | 1.70 | 91.46 | 155.04 |
| 3 | 0.59 | 1.04 | 1.76 | 254.24 | 448.15 |
| 4 | 1.19 | 0.82 | 0.69 | 126.05 | 86.86 |
| 5 | 1.02 | 0.88 | 0.86 | 147.06 | 126.87 |
| 6 | 1.65 | 3.61 | 2.19 | 90.91 | 198.90 |
| 7 | 0.98 | 1.91 | 1.95 | 153.06 | 298.31 |
| 8 | 0.83 | 1.57 | 1.89 | 180.72 | 341.85 |
| 9 | 1.20 | 2.67 | 2.23 | 125.00 | 278.13 |
| 10 | 1.17 | 2.29 | 1.96 | 128.21 | 250.93 |
| 11 | 1.22 | 3.02 | 2.48 | 122.95 | 304.35 |
| Mean | 1.17 | 2.13 | 1.80 | 138.94 | 246.86 |
| SD | 0.30 | 0.91 | 0.50 | 46.08 | 101.99 |

dissection, aortic cross-clamping, revascularization and retroperitoneal tumour dissection, would influence blood flow in the extradural and spinal cord.

(c) The volume of extradural fat, to which sufentanil is rapidly and firmly bound, is variable. The amount of the drug transferred to the central circulation and CSF may differ between individuals.

Thus sufentanil, injected either intrathecally or extradurally, may rapidly, but variably, gain access to the venae cavae via the valveless extradural venous plexuses and the meningo-arachnoidian plexus. After $C_P$max is reached (which occurs in the first 15 min after extradural and intrathecal injection), a slow decline in plasma concentration occurs as a result of the high binding of sufentanil to specific and non-specific receptors until elimination is complete. Small differences in $C_P$ after ES and IS could be produced by variation in the amount of sufentanil retained in the extradural space and CSF. The low fraction of sufentanil that reached the central circulation after ES and IS up to the time of tracheal extubation is an indication of a relatively long transit time of the drug in the extradural space and spinal cord. MRT, which was similar for the ES and IS groups, indicated that 63.2 % of plasma sufentanil was eliminated in about 3 h. MRT values after ES and IS were about twice as long as after IVS, because of the slow rate of absorption of sufentanil into the central circulation from the extradural and intrathecal spaces. The larger $Vd^{ss}$ after ES and IS than after IVS shows, also, that sufentanil binds to additional tissue components, notably extradural fat and the spinal cord.

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# INFLUENCE OF THE LUMBAR INTERSPACE CHOSEN FOR INJECTION ON THE SPREAD OF HYPERBARIC 0.5% BUPIVACAINE

S. M. LOWSON, J. BROWN AND C. J. WILKINS

## SUMMARY

*Forty patients undergoing elective Caesarean section were allocated randomly to receive hyperbaric 0.5% bupivacaine 2.5 ml at either the L2–3 (n = 20) or L4–5 (n = 20) interspace. Spinal injection was performed with a 29-gauge needle in 38 patients and a 25-gauge needle in two. The onset time to analgesia at T10 and T6 was significantly faster and the level of analgesia at 5 and 10 min after injection significantly higher after injection at L2–3. Maximum height and range of analgesia, the level of analgesia at 15 and 20 min after injection and the number of episodes of hypotension were not significantly different between the two groups. One case of post-dural puncture headache was recorded after use of a 29-gauge needle. Overall, the choice of lumbar interspace influenced the rate of onset of analgesia, but not the final dermatomal level (mean and range) of analgesia achieved.*

**KEY WORDS**

*Anaesthetic techniques spinal. Anaesthetics, local: bupivacaine.*

Subarachnoid injection of local anaesthetic is an established method of providing regional analgesia for patients undergoing Caesarean section. As this is a single injection technique, it is vital to be able to predict reliably the spread of the injected local anaesthetic solution in the CSF and therefore the level of analgesia obtained. Spread of local anaesthetic in the CSF is dependent on several factors, one of which is the spinal interspace chosen for injection [1]. Studies on the influence of the lumbar interspace on the spread of plain 0.5% bupivacaine have produced contradictory results [2–4]. We decided, therefore, to investigate the influence of the lumbar interspace on the spread of hyperbaric 0.5 % bupivacaine.

## PATIENTS AND METHODS

We studied 40 patients (ASA I) undergoing elective Caesarean section with no contraindication to a regional technique. All patients were informed of the nature of the study, which was approved by the local Ethics Committee.

Patients were allocated randomly to receive hyperbaric 0.5% bupivacaine 2.5 ml at either the L2–3 ($n = 20$) or L4–5 ($n = 20$) interspace. On arrival of the patient in the anaesthetic room, a peripheral i.v. cannula was inserted and Hartmann's solution 1 litre was infused rapidly. In all but two patients, spinal injection was performed with a 29-gauge needle, by anaesthetists experienced in the use of such a needle. In the remaining two patients, insertion of the 29-gauge needle proved technically difficult and a 25-gauge needle was used. Free flow of CSF down the spinal needle was obtained before injection of the local anaesthetic solution. Hyperbaric 0.5% bupivacaine was injected via a midline approach, without barbotage, over a minimum of 30 s with the patient in the sitting position. Palpation of the iliac crest was performed to confirm the position of the 4th lumbar vertebra. Completion of the injection was taken as zero time and patients were immediately placed supine, horizontal with a left lateral tilt. Pinprick analgesia (with a 25-gauge needle) and motor block (Bromage scale 0–3 [5]), were tested at 1-min intervals for the first 10 min and 2-min intervals thereafter up to 20 min, at which time patients were taken into the operating

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TABLE I. *Patient characteristics (mean (range or SD))*

| | Group L2–3 ($n = 20$) | Group L4–5 ($n = 20$) |
|---|---|---|
| Age (yr) | 27.4 (18–36) | 26.8 (18–34) |
| Weight (kg) | 72.2 (9.2) | 67.4 (7.7) |
| Height (cm) | 158.4 (6.8) | 157.2 (5.5) |

theatre. Routine testing of pinprick analgesia and motor block was not performed until completion of the operation, in order to avoid disturbing the mother during birth of her child.

Arterial pressure was measured with an automatic recorder (Datascope: Accutor). Three recordings were taken before the spinal injection, in order to obtain a mean baseline arterial pressure, and at 2-min intervals thereafter. Episodes of hypotension (systolic arterial pressure < 100 mm Hg) were recorded and treated with a further 500 ml of Hartmann's solution and administration of i.v. ephedrine. The dose of ephedrine required to treat hypotension was recorded.

Subjective sensation of discomfort or shortness of breath were noted. All patients were seen by a member of the anaesthetic team for a minimum of 3 days after operation and were questioned specifically for occurrence and nature of any headache experienced.

Data were analysed by Student's *t* test and Wilcoxon rank sum test; $P < 0.05$ was considered significant.

## RESULTS

There was no significant difference between the two groups in age, height or weight (table I). There was no significant difference in the maximum height of pinprick analgesia or the extent of analgesia produced by injection of hyperbaric 0.5% bupivacaine 2.5 ml at either L2–3 or L4–5 (table II). Spinal injection at L2–3 produced a significantly faster onset of analgesia at T10 and T6, and motor block (scale 1) and analgesia at a significantly higher level at 5 and 10 min after injection (fig. 1). There was no significant difference in the levels at which analgesia was obtained at 15 and 20 min after injection or in the onset time to complete motor block (scale 3) between the two groups. Despite the lateral tilt, no patient developed a block that varied by more than two segments between the two sides, the majority of blocks being symmetrical. There was no significant difference between the two groups in the mean level of analgesia after operation.

Hypotension occurred in 14 patients in group L2–3 and 13 patients in group L4–5. The mean (SD) dose of ephedrine required to treat hypotension was 9.6 (8.0) mg for group L2–3 and 8.5 (9.2) mg for group L4–5 (not significant).

Episodes of discomfort were recorded in four patients in group L2–3 and six patients in group L4–5. All occurred after delivery, were associated with suturing of the uterus or abdominal wall and were relieved rapidly by alfentanil 0.25–0.5 mg i.v. Discomfort was not associated with lower levels of block. The range of blocks in patients who experienced discomfort was T3–6 in the L2–3 group and T3–5 in the L4–5 group.

Dyspnoea was noted by three patients in each group. The levels of block in patients complaining of dyspnoea were T2–5 in the L2–3 and T2–3 in the L4–5 group. It thus appeared that, provided an adequate and not excessive extent of analgesia was achieved, discomfort or dyspnoea occurred independently of block height.

Post-dural puncture headache occurred in two patients: one after the use of a 25-gauge needle

TABLE II. *Maximum cephalad spread of analgesia (mean (SD) [range]), time to onset of analgesia to T10 and T6, time to onset of motor block and extent of analgesia at the end of the operation. *Significant difference between the two groups* ($P < 0.05$)

| | Group L2–3 | | Group L4–5 |
|---|---|---|---|
| Maximum cephalad spread | T2.8 (0.8) [2–6] | | T3.0 (1.3) [2–7] |
| Onset time to T10 (min) | 5.1 (1.5) | * | 6.9 (2.1) |
| Onset time to T6 (min) | 8.2 (2.2) | * | 10.2 (3.2) |
| Onset of motor block (min) | | | |
| Scale 1 | 2.7 (1.0) | * | 5.2 (2.3) |
| Scale 3 | 7.6 (2.6) | | 9.3 (3.0) |
| Extent of analgesia at end of operation | T4.2 (1.0) | | T4.6 (1.5) |
| Time to end of operation (min) | 56 2 (11.6) | | 64.7 (9.2) |

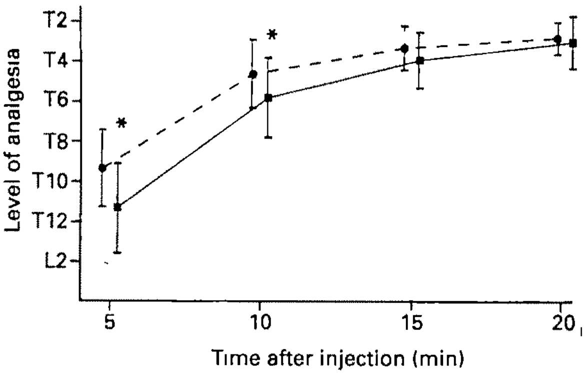

FIG 1 Mean (SD) level of analgesia at 5, 10, 15 and 20 min after injection for groups L2–3 (●– –●) and L4–5 (■——■). *Significant difference between groups ($P < 0.05$)

and one after a 29-gauge needle. Both were mild, non-disabling, had a maximum duration of 72 h and were relieved by oral analgesics.

## DISCUSSION

The initial cephalad spread of hyperbaric 0.5 % bupivacaine was faster after spinal injection at the L2–3 interspace as demonstrated by the difference in level of analgesia at 5 and 10 min after injection, onset time to block at T10 and T6 and onset time of motor blockade (scale 1). Thereafter, it appeared that the spread of the local anaesthetic solution injected at L4–5 was similar to that injected at L2–3, as demonstrated by the non-significant difference in the levels of analgesia at 15 and 20 min, the onset time to complete motor block (scale 3) and the maximum height and range of analgesia obtained. Although the level of pinprick analgesia was not examined routinely beyond 20 min after injection, there was no evidence to suggest that significant cephalad spread of analgesia occurred after this time. In two previous studies of the spread of hyperbaric 0.5 % bupivacaine [6, 7], the mean time to produce the maximum upper segmental level of analgesia was 15 min. Overall, it appeared from our study that the lumbar interspace chosen for spinal injection was of little importance to the height of the block produced.

A possible explanation for these findings is the position of the spinal interspace chosen for injection in relation to the maximum height of the lumbar curvature at L3. Spinal injection at the L2–3 interspace deposits the hyperbaric anaesthetic solution on the cranial side of the maximum height of the lumbar curvature at L3, where it spreads cephalad under the influence of gravity. However, a hyperbaric solution injected at L4–5 must first spread cephalad by bulk displacement of CSF, diffusion, or both, before gravity induces further cephalad spread. The mechanism whereby the spread of local anaesthetic solution at L4–5 "caught up" with that injected at L2–3 is not known. However, this catching up may explain the fact that the number of episodes of hypotension and the mean dose of ephedrine required to treat hypotension did not differ significantly between the two groups.

In an investigation of the spread of hyperbaric 0.5 % bupivacaine in the CSF, Sundnes and colleagues [6] found that the lumbar interspace had no influence on the maximum upper segmental level of analgesia or the time taken to reach this level. These workers did not report the time taken to reach sub-maximal levels of analgesia, whereas in the present study we were particularly interested in the onset time to block at T6 and T10. T6 is the level of analgesia considered adequate to provide analgesia for Caesarean section, although it has been suggested [8] that a T10 level may be sufficient.

In the study by Russell and Holmquist [7], the injection of hyperbaric or plain 0.5 % bupivacaine 2.5 ml with the patient in the lateral position produced maximum heights of analgesia greater than in the present study, with blocks rising to the cervical dermatomes in 25 % of patients. In the present study no patient developed objective loss of pinprick analgesia above the T2 dermatome. Although one patient complained of a tingling sensation unilaterally along the ulnar border of the forearm, the sensation was short lasting (less than 10 min) and was not associated with loss of pinprick analgesia over this area. Our technique differed from that of Russell in two ways: the size of spinal needle and the position of the patient when the hyperbaric local anaesthetic solution was injected. We feel the latter is probably the significant factor. The slow injection of hyperbaric 0.5 % bupivacaine with the patient in the sitting rather than the lateral position may limit cephalad spread of local anaesthetic, so reducing the incidence of blocks reaching the cervical dermatomes. Certainly, spinal injection with the patient in the sitting rather than the lateral position appears to limit the rate of cephalad spread of the hyperbaric local anaesthetic solution. At 5 min after injection the median level of block in the present study was T10 (L2–3) and T12 (L4–5), compared with T3 in the study by Russell [7].

In this study we found that one patient of 38 in whom spinal injection was performed with a 29-gauge needle developed a post-dural puncture headache and this was mild in nature. In two patients (5%) location of the subarachnoid space using a 29-gauge needle proved technically difficult; this is comparable to the 8% failure rate found by Flaatten and colleagues [9] in their study on the use of the 29-gauge spinal needle.

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# DETERMINANTS OF THE REVERSAL TIME OF COMPETITIVE NEUROMUSCULAR BLOCK BY ANTICHOLINESTERASES

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## SUMMARY

*We have assessed, in 200 patients, the determinants of the reversal time of competitive neuromuscular block by anticholinesterase when alcuronium and atracurium neuromuscular block were antagonized by neostigmine 0.04 and 0.08 mg kg$^{-1}$ and edrophonium 0.5 and 1.0 mg kg$^{-1}$. A biexponential relationship was found between the reversal time (time from injection of anticholinesterase to a train-of-four ratio of 70%) and the degree of neuromuscular block at reversal (all groups;* F *ratio,* $P < 0.05$*). Reversal time was determined by two processes: direct antagonism by the anticholinesterase and spontaneous recovery of the neuromuscular blocking agent, with the latter becoming the major determinant at profound levels of neuromuscular block (0–10% of control twitch height). Neostigmine, in the doses studied, appeared to have a higher "ceiling" of neuromuscular block which it completely antagonized, although edrophonium had a more rapid onset of action. The reversal time for alcuronium became progressively longer relative to atracurium as neuromuscular block increased because of the slower spontaneous recovery rate. Avoidance of profound neuromuscular block at the completion of surgery is required to ensure reliable antagonism of the block within 5–10 min by an anticholinesterase. Neostigmine 0.08 mg kg$^{-1}$ was found to be the most effective agent in antagonizing profound neuromuscular block.*

***KEY WORDS***

*Antagonists, neuromuscular relaxants: edrophonium, neostigmine Neuromuscular relaxants: atracurium, alcuronium*

Recommendations from studies on the optimal dose of anticholinesterases are conflicting. Some authors recommend edrophonium 0.5 mg kg$^{-1}$ [1, 2] or 1–1.5 mg kg$^{-1}$ [3–5], while others recommend neostigmine [6–8]. It is difficult to compare these studies directly, as there were differences in anaesthetic technique, method of recording neuromuscular block, end-point defining recovery, and level of neuromuscular block when anticholinesterase was administered.

The competitive neuromuscular blocking agent, the degree of block, the type of anticholinesterase and its dose have been identified as important determinants of the time for adequate recovery [1–8]. However, how these factors interact has not been determined.

This study was undertaken to examine the interaction of factors which govern antagonism of an intermediate and long acting competitive neuromuscular blocking agent. Neuromuscular block was achieved with the long acting agent alcuronium or the intermediate acting agent atracurium, and was antagonized at various degrees of block by either edrophonium or neostigmine.

## PATIENTS AND METHODS

We studied 200 patients undergoing general anaesthesia (table I). The study was approved by the hospital Ethics Committee. Patients were allocated to receive neostigmine 0.04 mg kg$^{-1}$ and atropine 0.02 mg kg$^{-1}$, neostigmine 0.08 mg kg$^{-1}$ and atropine 0.03 mg kg$^{-1}$, edrophonium 0.5 mg

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TABLE I. *Patient characteristics and drugs received*

| Drug group | Sex (M/F) | Age (yr) | Weight (kg) |
|---|---|---|---|
| Edrophonium 0.5 mg kg$^{-1}$ | | | |
| Alcuronium ($n$ = 25) | 12/13 | 24–76 | 68.3 (11.7) |
| Atracurium ($n$ = 25) | 13/12 | 24–78 | 72.0 (14.6) |
| Edrophonium 1.0 mg kg$^{-1}$ | | | |
| Alcuronium ($n$ = 25) | 8/17 | 17–73 | 67.6 (14.7) |
| Atracurium ($n$ = 25) | 12/13 | 19–73 | 66.4 (17.8) |
| Neostigmine 0.04 mg kg$^{-1}$ | | | |
| Alcuronium ($n$ = 25) | 8/17 | 22–76 | 72.1 (15.1) |
| Atracurium ($n$ = 25) | 9/16 | 19–72 | 67.0 (15.2) |
| Neostigmine 0.08 mg kg$^{-1}$ | | | |
| Alcuronium ($n$ = 25) | 9/16 | 19–76 | 67.4 (11.2) |
| Atracurium ($n$ = 25) | 12/13 | 17–78 | 67.3 (13.0) |

kg$^{-1}$ and atropine 0.01 mg kg$^{-1}$, or edrophonium 1.0 mg kg$^{-1}$ and atropine 0.02 mg kg$^{-1}$. There were 50 patients in each anticholinesterase dosage group, with 25 patients being given each competitive neuromuscular blocking agent. Patients were excluded from the study if they had a history of unusual sensitivity to neuromuscular blocking agents, evidence of neuromuscular disease, electrolyte abnormalities, or renal or liver impairment. In addition, patients were excluded if the neuromuscular monitoring used during the procedure was found to be inaccurate, as detailed below.

The electromyogram (EMG) of the first dorsal interosseous muscle to repetitive supramaximal train-of-four (TOF) stimulation of the ulnar nerve every 10 s was measured and recorded by a Datex Relaxograph. The test hand was immobilized with no resting tension and wrapped in a warm towel. The EMG was calibrated after induction of anaesthesia, but before the administration of any neuromuscular blocking agent, by establishing a control twitch height to the first stimulus of a TOF stimulation (100 % T1c) and a TOF ratio of the first to the fourth response (T1 : T4). Muscle paralysis was produced initially with suxamethonium or a bolus dose of atracurium or alcuronium and maintained thereafter with the competitive neuromuscular blocking agent. The anaesthetic technique was chosen by the responsible anaesthetist in accordance with standard clinical practice. Table II details the anaesthetic data for the different neuromuscular blocking agent–anticholinesterase groups.

At the end of the surgical procedure, residual neuromuscular block was antagonized by an anticholinesterase, the drug and dose depending on the group to which the patient was allocated. T1 : T4 = 70 % was defined as indicating adequate clinical recovery from neuromuscular block [9]. A continuous recording was made of the first and fourth twitch response of the EMG from time of administration of the anticholinesterase to recovery. The first twitch response of the EMG at time of administration of the anticholinesterase (%T1.reversal) and the time taken from injection of the anticholinesterase to T1 : T4 greater than 70 % (reversal time) were noted. Anaesthesia was discontinued thereafter, but EMG monitoring continued as long as possible. The first twitch response of the EMG at this time (%T1.recovery) was recorded.

Allowance for drift in calibration of the EMG

TABLE II. *Anaesthetic data (mean* (SD)). *Anaesthesia was categorized as being maintained with either volatile (V) or i.v. (I) agents*

| Drug group | Anaesthesia V/I | Duration (min) | Suxamethonium ($n$) | Dose of blocking drug (mg) |
|---|---|---|---|---|
| Edrophonium 0.5 mg kg$^{-1}$ | | | | |
| Alcuronium | 24/1 | 110 (53) | 11 | 18.0 (6.4) |
| Atracurium | 19/6 | 108 (58) | 5 | 60.3 (29.2) |
| Edrophonium 1.0 mg kg$^{-1}$ | | | | |
| Alcuronium | 22/3 | 85 (30) | 8 | 16.5 (3.2) |
| Atracurium | 15/10 | 86 (67) | 9 | 41.5 (22.3) |
| Neostigmine 0.04 mg kg$^{-1}$ | | | | |
| Alcuronium | 23/2 | 88 (39) | 13 | 17.7 (5.9) |
| Atracurium | 19/6 | 81 (34) | 10 | 42.7 (15.2) |
| Neostigmine 0.08 mg kg$^{-1}$ | | | | |
| Alcuronium | 24/1 | 86 (48) | 8 | 17.0 (5.2) |
| Atracurium | 18/7 | 112 (71) | 8 | 54.0 (29.0) |

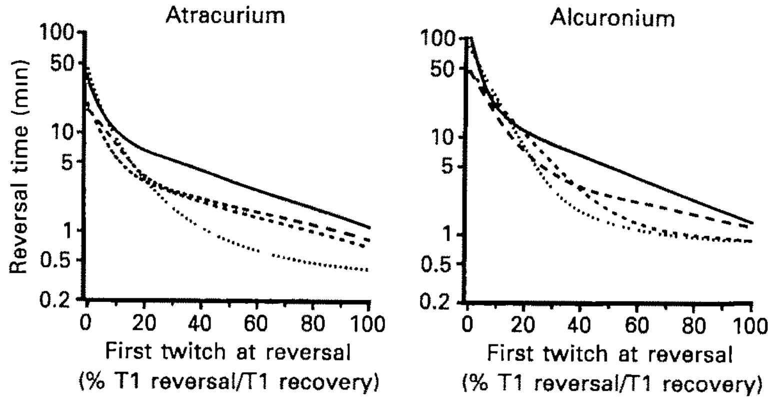

FIG. 1. Biexponential relationship between reversal time (time from injection of the anticholinesterase until a train-of-four ratio of 70%) and the degree of neuromuscular block at time of administration of the anticholinesterase (first twitch height %T1.reversal/T1.recovery) for antagonism of atracurium and alcuronium by edrophonium 0.5 mg kg$^{-1}$ (----) and 1.0 mg kg$^{-1}$ (....) and neostigmine 0.04 mg kg$^{-1}$ (——) and 0.08 mg kg$^{-1}$ (—) (in each case inclusion of the biexponential regression line; *F* ratio, $P < 0.05$).

was made by taking %T1.recovery as the control first twitch height [10]. Using this criterion, the depth of neuromuscular block at reversal was %T1.reversal/T1.recovery. Patients were excluded from the study if excessive drift in the EMG calibration had occurred as indicated by a %T1.recovery of less than 60% T1c.

Curve fitting was performed with the extended least squares computer software MK-MODEL (Elsevier-BIOSOFT). The curves of reversal time *vs* depth of neuromuscular block at time of administration of the anticholinesterase for the different groups were fitted with mono- and biexponential curves. The justification for inclusion of the second exponential was tested with the *F* ratio, $P < 0.05$ [11].

Patient and anaesthetic data were compared with ANOVA and chi-square analysis. Three way-ANOVA and unpaired Student's *t* test with Bonferroni correction for multiple comparisons were used to compare reversal data at profound and light block. $P < 0.05$ was defined as significant. Data are presented as mean (SD).

## RESULTS

The biexponential relationships between reversal time and the degree of neuromuscular block at time of administration of the anticholinesterase are illustrated in figure 1 for antagonism of atracurium and alcuronium neuromuscular block by edrophonium 0.5 and 1.0 mg kg$^{-1}$ and by neostigmine 0.04 and 0.08 mg kg$^{-1}$. This biexponential relationship was consistent with reversal time being determined by two processes. A second slower process became a determinant of the reversal time at more profound levels of neuromuscular block.

Analysis of the individual EMG recordings of antagonism of neuromuscular block by anticholinesterase showed that edrophonium had an initial peak effect within 1–3 min, and thereafter recovery occurred at a slow rate during a plateau phase. In contrast, neostigmine produced a more gradual and sustained antagonism, with the plateau phase discernible only after 6–10 min. Figure 2 illustrates typical recordings of the antagonism of an alcuronium-induced neuromuscular block by neostigmine 0.04 mg kg$^{-1}$ and edrophonium 0.5 mg kg$^{-1}$. The plateau phase was absent when small degrees of block were antagonized. The plateau phase was discernible in the antagonism of deep neuromuscular block (0–10% T1.reversal/T1.recovery) in patients from all groups. The rate of recovery of alcuronium neuromuscular block during the plateau phase was slower and more variable than that of atracurium. Figure 3 illustrates an example of very slow recovery of alcuronium neuromuscular block during the plateau phase following antagonism of the block by edrophonium 0.5 mg kg$^{-1}$ (data from this patient were not included in other analyses because recovery was not recorded until T1:T4 > 70%).

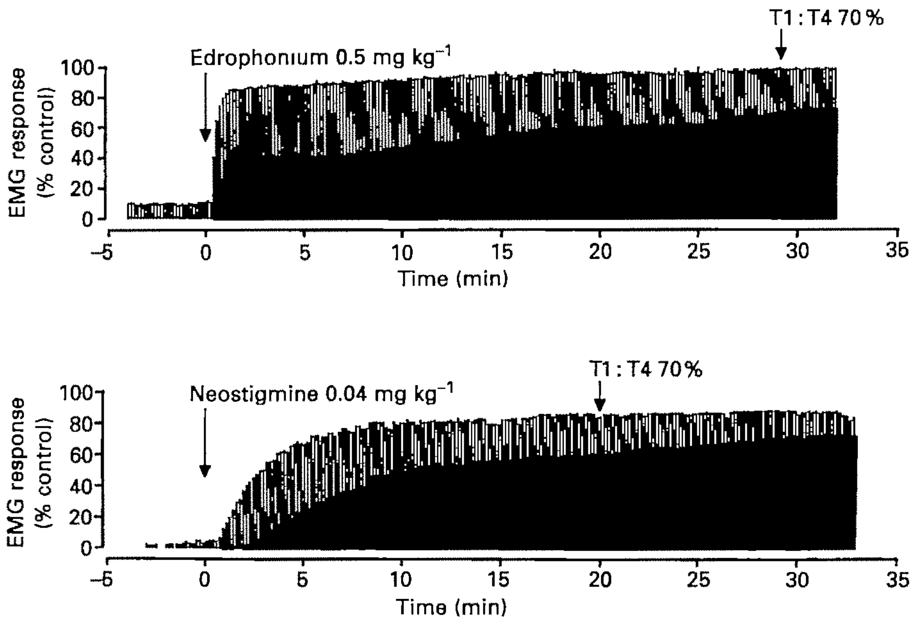

FIG. 2. Recordings of the first and fourth twitch response of the EMG from two patients during antagonism of profound alcuronium block. The top tracing is from a patient in whom block was antagonized by edrophonium 0.5 mg kg$^{-1}$ at 11 % twitch height (%T1.reversal/T1.recovery). Adequate recovery, as defined by a train-of-four ratio (T1·T4) of 70 %, occurred 29 min after administration of the edrophonium. The lower tracing is from a patient in whom block was antagonized by neostigmine 0.04 mg kg$^{-1}$ at 5 % twitch height. A T1 : T4 of 70 % occurred 20 min after injection of the neostigmine.

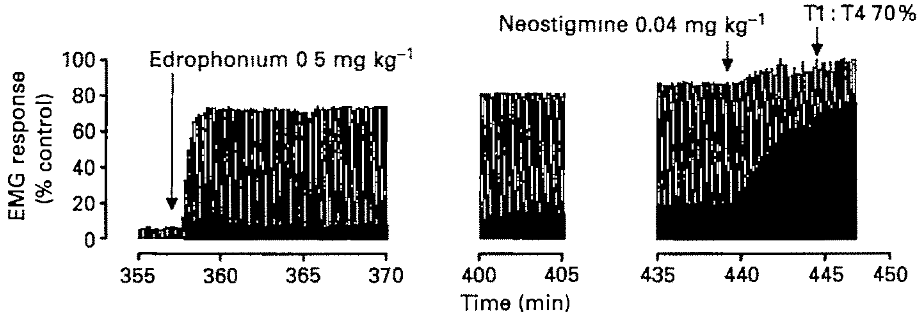

FIG. 3. Excerpts from the recording of the first and fourth twitch response of the EMG from a 55-yr-old female undergoing propofol anaesthesia, during antagonism of an alcuronium block from 7 % twitch height (%T1.reversal/T1.recovery) by edrophonium 0.5 mg kg$^{-1}$. The block was antagonized after 357 min of surgery during which the patient received 55 mg of alcuronium. The block recovered to 73 % twitch height (T1 : T4 9 %) within 2 min, but thereafter had a very slow recovery during the plateau phase. After a further 83 min, the block had recovered to 87 % twitch height (T1 : T4 20 %). At that time, the block was antagonized by neostigmine 0.04 mg kg$^{-1}$ and recovered to 100 % twitch height (T1 : T4 > 70 %) within 5 min.

Table III details the reversal time for antagonism of profound (0–10 % T1.reversal/T1.recovery) and light (> 30 % T1.reversal/T1.recovery) neuromuscular block for the different neuromuscular blocking agent–anticholinesterase groups. There were significant differences between the reversal times at both profound and light block for neuromuscular blocking agents, anticholinesterases and doses (in each case, three-way ANOVA, $P < 0.05$).

TABLE III. *Reversal times (mean (SD)) for the different neuromuscular blocking agent–anticholinesterase groups at profound (0–10% T1.reversal/T1.recovery) and light (> 30% T1.reversal/T1.recovery) block.* **Student's* t *test with Bonferroni correction for multiple comparisons*: $P < 0.05$

| | Profound block | | Light block | |
|---|---|---|---|---|
| | *n* | Reversal time (min) | *n* | Reversal time (min) |
| Atracurium | | | | |
| Neostigmine 0.04 mg $kg^{-1}$ | 7 | 20.5 (13.1)* | 10 | 3.1 (1.9)* |
| Neostigmine 0.08 mg $kg^{-1}$ | 13 | 9.0 (4.9) | 6 | 1.7 (0 9) |
| Edrophonium 0.5 mg $kg^{-1}$ | 7 | 18.0 (9.1) | 11 | 1.5 (0.8) |
| Edrophonium 1.0 mg $kg^{-1}$ | 10 | 11.2 (6.7) | 7 | 1.1 (0.6) |
| Alcuronium | | | | |
| Neostigmine 0.04 mg $kg^{-1}$ | 7 | 31.4 (15.5) | 10 | 6.1 (3.7)* |
| Neostigmine 0.08 mg $kg^{-1}$ | 10 | 25.4 (17.6)* | 6 | 2.3 (1.2) |
| Edrophonium 0.5 mg $kg^{-1}$ | 7 | 53.4 (25.3) | 8 | 1.6 (0.7) |
| Edrophonium 1.0 mg $kg^{-1}$ | 7 | 39.4 (19.9) | 12 | 1.9 (1.0) |

The administration of anticholinesterase did not induce neuromuscular block in any patient. In patients administered anticholinesterase at almost complete spontaneous recovery of the neuromuscular block, the block quickly recovered and remained at T1:T4 > 70% with EMG monitoring continuing for up to 25 min.

## DISCUSSION

We have observed a biexponential relationship between the degree of competitive neuromuscular block and the time to adequate recovery following administration of an anticholinesterase. This biexponential relationship may be considered to reflect the differing contributions of the two major processes which determine the reversal time of a neuromuscular block. Direct antagonism of the block by the anticholinesterase was the primary process at small degrees of block (> 30% T1.reversal/T1.recovery). Spontaneous recovery of the neuromuscular blocking agent was the predominant process determining reversal time at high degrees of neuromuscular block (0–10% T1.reversal/T1.recovery). The anticholinesterase had a "ceiling" to the extent of block which it could antagonize completely. When antagonism of degrees of neuromuscular block greater than the ceiling was attempted, the block continued to recover slowly during a plateau phase following the peak antagonistic effect of the anticholinesterase. This plateau represented a balance between spontaneous recovery and the waning antagonistic effect of the anticholinesterase. The duration of the antagonistic effect of edrophonium and neostigmine was a secondary determinant of the reversal time of deep neuromuscular block, as their duration of action was longer than that of the competitive neuromuscular blocking agents [2, 12–14].

The clinically significant difference in the reversal times of atracurium and alcuronium occurred at profound levels of neuromuscular block. The slower spontaneous recovery of alcuronium caused the reversal times for alcuronium to increase relative to atracurium. The recovery time (time for spontaneous recovery of neuromuscular block from 25% to 75% of control twitch height) for an intubating dose of atracurium is 20 min and is relatively independent of the size of the dose [13]. The recovery time for an intubating dose of alcuronium is 45 min and may increase to 112 min or longer after repetitive doses because of its cumulative properties [14, 15]. The reversal time of profound neuromuscular block following repetitive doses of alcuronium may be extremely prolonged. The reversal characteristics of alcuronium and atracurium may be considered as generally representative of long and intermediate acting competitive neuromuscular blocking agents [1–8]; the superior antagonizing characteristics of intermediate acting neuromuscular blocking agents explains the observed lower incidence of residual block associated with their use [16].

The anticholinesterases edrophonium and neostigmine have important differences in their ability to antagonize competitive neuromuscular block. The faster onset of antagonism by edrophonium in the present study is consistent with the observations of times to peak antagonism of a tubocurarine block of 0.8–2.0 min for edrophonium 0.5 mg kg$^{-1}$, and 7–11 min for neostigmine 3 mg/70 kg [2, 12]. Hence at small degrees of block, when antagonism of the block by an anticholinesterase was the predominant process determining reversal time, edrophonium produced a shorter reversal time than neostigmine. At profound levels of neuromuscular block the converse applied, with neostigmine having a shorter reversal time. This may reflect the administration of a larger effective dose of neostigmine. The dosage of neostigmine relative to edrophonium is difficult to compare, as their dose–response curves are not parallel [2, 16]. Alternatively, this may be a reflection of the supposed greater efficacy of neostigmine [17]. The shorter reversal times of profound block by neostigmine may also be a reflection of its longer duration of action [2, 12].

The effect of dose of anticholinesterase on reversal time is complex. Dosage determines the ceiling of neuromuscular block which the anticholinesterase can directly antagonize. Increasing the dose of edrophonium from 0.5 to 1.0 mg kg$^{-1}$ increased the ceiling of neuromuscular block which it could antagonize directly. The dose of anticholinesterase may be important also in determining the reversal time of small degrees of block, below the ceiling of the anticholinesterase, for anticholinesterases which have a slow onset of action. Increasing the dose of neostigmine from 0.04 to 0.08 mg kg$^{-1}$ decreased the reversal time of low levels of block. By determining the duration of antagonism, the dosage of anticholinesterase may affect also the reversal time of block deeper than the ceiling of the anticholinesterase. Theoretically, the effect of dosage in this circumstance would be most pronounced with edrophonium, because of its shorter duration of action.

Concern about the administration of large doses of anticholinesterases inducing muscle weakness, particularly when antagonizing agents of intermediate duration of action such as atracurium at almost complete spontaneous recovery of the neuromuscular block, appears to be largely unfounded. An increase in tetanic fade has been observed after repeat administration of neostigmine 2.5 mg in the presence of a block which had fully recovered [18]. The significance of minor degrees of tetanic fade is difficult to assess, as fade may occur in the absence of neuromuscular blocking agents [19]. In this and other studies, in which neuromuscular block was assessed with TOF stimulation, there has been no evidence of muscle weakness being induced by an anticholinesterase, even when it was administered at near total recovery of the block [20, 21].

Understanding the processes which govern the reversal time of a competitive neuromuscular block by an anticholinesterase is the best way to ensure adequate recovery in all patients and avoid the potential complications of residual paralysis. The anaesthetist cannot rely on a given dose of an anticholinesterase to ensure rapid antagonism of a competitive block at the termination of surgery. The most important determinant of reversal time is the depth of neuromuscular block at the time of antagonism and this should determine the anticholinesterase and its dose. Another factor which should be considered is the type and dose of competitive neuromuscular blocking agent. When large doses of long acting competitive neuromuscular blocking agents are administered during surgery, it may be anticipated that antagonism of profound block by an anticholinesterase will be prolonged.

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# SYSTEMS ANALYSIS APPLIED TO INTRACRANIAL PRESSURE WAVEFORMS AND CORRELATION WITH CLINICAL STATUS IN HEAD INJURED PATIENTS

E. S. LIN, W. POON, R. C. HUTCHINSON AND T. E. OH

**SUMMARY**

*Intracranial pressure waveforms (ICPWF) in head injured patients vary with the nature and severity of injury. Clinical interpretation of ICPWF shape is not defined. Spectral analysis provides an objective method of measuring changes in waveform shape, but the indices most suitable for clinical use remain unknown. Spectral analysis has been applied to ICPWF recorded from 30 patients with head injury, classified on clinical grounds into good, poor and intermediate groups. Normalized indices derived from ratios of certain characteristics of the ICP waveform to those of the arterial pressure (AP) waveform, were different ($P < 0.05$) in all groups. A simple index examined was the harmonic count ratio (Nc:Na) which decreased with increasing severity of injury. ICP/AP harmonic transfer functions were derived, and demonstrated a peaked response in the range 10–12 Hz. Increasing attenuation of this peaked response occurred with increasing severity of injury. These results suggest that transfer functions may be a clinically useful index of intracranial conditions.*

**KEY WORDS**

*Brain. head injury Measurement techniques: spectral analysis Monitoring: intracranial pressure waveform*

Intracranial pressure (ICP) measurement remains the most commonly used technique for continuously monitoring intracranial conditions in neurosurgical patients. The mean ICP (MICP) is the usual variable monitored. However, clinical interpretation of increased MICP has some limitations. Although consistently increased MICP values (>40 mm Hg) correlate well with poor clinical status and outcome [1], this relationship is less predictable in patients with moderately increased values (20–30 mm Hg) [2]. In such cases, MICP measurements may fail to differentiate patients whose intracranial status is deteriorating from those who are stable or improving. The MICP may also prove unreliable by demonstrating a delayed response in the face of acute changes in intracranial conditions.

The pressure–volume relationship of the intracranial cavity has been investigated by some workers as a more useful index of intracranial status and prognosis. The intracranial elastance is represented by the slope of this curve ($dP/dV$). This may be determined by measuring the increase in ICP in response to a small volume challenge to the cerebrospinal fluid (CSF) space and may be referred to as the pressure–volume response (PVR). A pressure–volume index (PVI) also may be derived from a small injection into the CSF space. The PVI represents the volume of infusion required to increase the ICP 10 times and is calculated by assuming a logarithmic pressure–volume relationship [3, 4]. This improves predictive ability by locating the position of the intracranial cavity on the pressure–volume curve more accurately. However, such volume provocation tests are not suitable for repeated measurements because of their invasive nature, and cannot provide continuous monitoring.

A further alternative lies in the analysis of intracranial pressure waveforms (ICPWF) which

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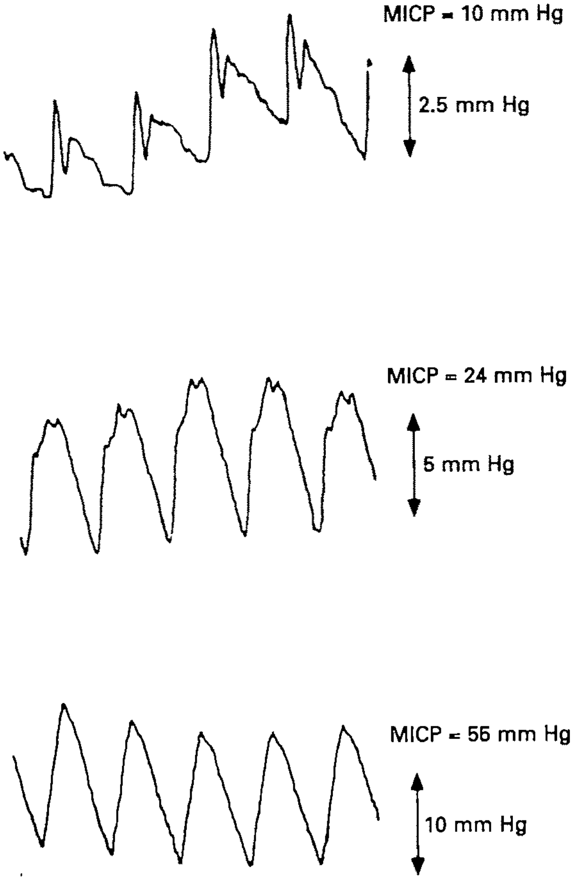

FIG. 1. Examples of varying intracranial pressure waveform (ICPWF) morphology recorded from different patients with head injury.

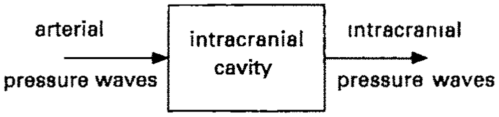

FIG. 2. Schematic diagram of intracranial cavity as a "black box" with arterial pressure waveform (APWF) as an input signal and ICPWF as the output signal.

may be recorded from the cerebral ventricles. These waveforms are commonly noted to vary in morphology with changes in severity and differing types of intracranial injury. Some examples of ICPWF with differing morphology recorded from different head injured patients are shown in figure 1. The application of spectral analysis to the ICPWF has been proposed by other workers [5, 6], and offers an objective method of assessing variations in waveform shape. This approach has the advantage of being comparatively non-invasive, and with modern technology can effectively provide on-line signal processing and continuous monitoring.

The interpretation of spectral changes in ICPWF for clinical purposes has not been established and correlations between changes in ICPWF spectra and neurological condition remain unknown. A useful approach involves the application of systems analysis to the intracranial cavity [7]. This provides a simple model to relate intracranial conditions to spectral changes in ICPWF. The basic concept used considers the intracranial cavity as a black box system with the arterial pressure (AP) signal as an input and the ICP signal as the output (fig. 2). The ratio of output (ICP) to input (arterial) spectra then yields a transfer function or frequency response for the intracranial cavity. This transfer function reflects hydrodynamic and physiological properties of the intracranial cavity which affect the formation of the ICPWF from the arterial pressure waveform (APWF) (fig. 3).

Animal studies demonstrate that ICP/AP transfer functions can be derived for normal intracranial conditions and that changes in transfer function can be produced by artificially increasing intracranial pressure or by inducing hydrocephalus [8].

In this study we have attempted to determine which ICPWF spectral variables are likely to be clinically useful, by applying spectral analysis to ICP signals obtained in head injured patients. We have also derived ICP/AP transfer functions from these patients and examined these in relation to the neurological condition of the patients as assessed by Glasgow Coma Score (GCS).

## PATIENTS AND METHODS

Following approval of the Research Ethics Committee of the Faculty of Medicine, 32 head injured patients were studied in the Intensive Care Unit (ICU) at the Prince of Wales Hospital. These patients were admitted after operation, having received neurosurgery (usually evacuation of a haematoma, contusionectomy, or both) which also included the insertion of an intraventricular catheter for ICP monitoring. In order to obtain spectral data in groups of patients with similar intracranial conditions, we grouped the patients, according to their GCS on admission to hospital, into "good" (GCS = 13–15), "intermediate" (GCS = 6–12) and "poor" (GCS = 3–5). The

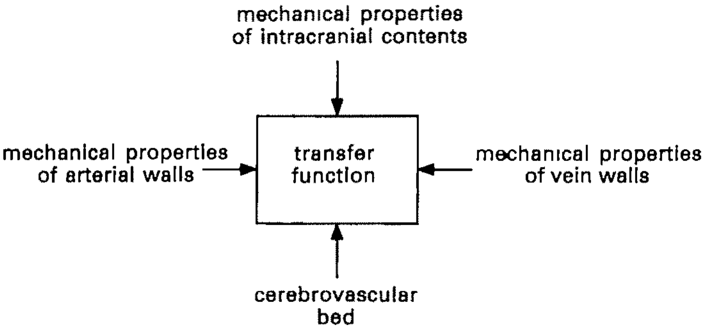
mechanical properties of intracranial contents
mechanical properties of arterial walls
transfer function
mechanical properties of vein walls
cerebrovascular bed

FIG. 3. Physiological and mechanical factors which determine the transfer function of the intracranial cavity.

patients were reassessed later, on discharge from the ICU after data collection was completed. Patients who underwent a marked change in neurological status so that initial and final GCS scores did not correspond were rejected. This ensured that the ICPWF recorded were grouped consistently according to GCS assessment over the period of data collection. Clinical assessment during this period was often difficult as patients were usually sedated and undergoing artificial ventilation.

The management of the patients in the ICU followed standard practice including sedation (morphine infusion with or without midazolam infusion) with and without neuromuscular block (atracurium), mechanical ventilation (maintaining $Pa_{CO_2}$ 3.5–4.5 kPa) for periods ranging from 12 h to several days, depending on severity of injury and clinical condition of the patient. Intra-arterial pressure monitoring (Deseret 8060 transducers) was routinely applied to all patients as part of normal management.

ICPWF were recorded (Hi-corder 8820, Hioki, Japan) initially on admission of each patient to the ICU and thereafter recordings were made at 12- or 24-h intervals. Simultaneous recordings were made of the radial APWF when ICPWF were recorded. Data were analysed on site using the built-in fast Fourier transform (FFT) facility of the recorder to provide an immediate hard copy of the APWF and ICPWF power spectra. In addition, derived power spectra were stored in an IBM-compatible microcomputer for further analysis and derivation of transfer functions.

### *Signal processing*

ICP and AP signals were monitored using Deseret 8060 pressure transducers with a linear response over the range −50 to 300 mm Hg and a flat frequency response to 125 Hz. Signal conditioning was through the ICU monitoring system (Simonsen & Weel) with cut off filters set to 100 Hz and re-calibrated manometrically each morning before recordings were made.

The FFT routine used by the signal recorder stored 20-s signal epochs and performed 1024 sample FFT on the signal using Hanning windowing. These settings yielded spectra over a frequency range of 0–23.4 Hz.

Examples of ICPWF power spectra are illustrated in figure 4: this shows how the derived power spectra were composed of harmonic peaks or spikes. The power spectra for corresponding epochs of arterial pressure waveform consisted also of a fundamental component accompanied by harmonic spikes.

Spectral parameters derived from the ICPWF consisted of:

(i) a simple harmonic spike count (Nc), taken relative to a baseline 60 dB down from the maximum peak amplitude recorded in the power spectrum;

(ii) a spectral edge (F90c) below which 90% of the power in the spectrum was contained;

(iii) the centroid frequency (HFCc) of a "high frequency band" between 4 and 15 Hz as defined by Bray and colleagues [5].

Corresponding AP spectral parameters Na, F90a and HFCa were determined also from the radial arterial pressure signals: "normalized" indices could then be calculated by taking the ratios Nc:Na, F90c:F90a and HFCc:HFCa.

In this way, a three-way comparison has been made between the standard monitoring indices of MICP and cerebral perfusion pressure (CPP), the spectral parameters obtained solely from the

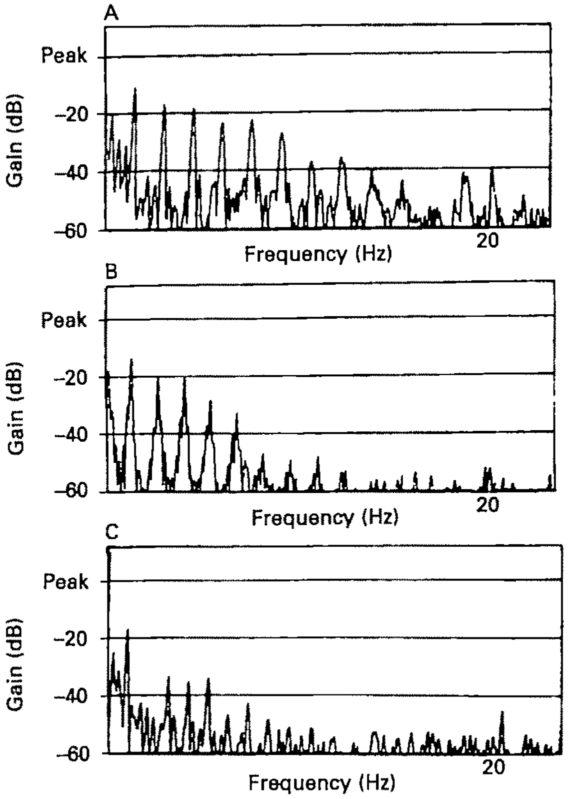

FIG. 4. Examples of IPCWF spectra from the good (A), intermediate (B) and poor (C) patient groups.

ICPWF spectra, and the normalized spectral parameters derived from both ICPWF spectra and AP spectra. These sets of indices have been compared in their ability to distinguish between three groups of patients as defined by their presenting GCS.

The spectral analysis of the ICP and AP signals has been extended further by determining the amplitude transfer functions. These were obtained from the ratio of corresponding harmonic spike amplitudes in the individual power spectra. Ideally, a transfer function is a spectral response function which is continuous over the frequency range examined. However, if derived from periodic signals it may be approximated to by using the spectra of the "input" and "output" signals used as in this case.

Recordings have been analysed and spectral parameters averaged for each individual, with a total of more than 200 traces analysed. For each group, between subject SD were calculated, and statistical comparisons between patient groups were made with the Kruskal–Wallis test with an extension for multiple comparisons.

## RESULTS

The mean duration of stay in the ICU for each of 32 patients was 4.1 (SD 3.7) days. A total of more than 200 ICPWF and APWF spectra were analysed.

Classification of the patients according to GCS on admission to hospital corresponded well with their grouping according to GCS on discharge from the ICU (table I). Two patients deteriorated markedly during admission to ICU and their recordings were rejected. Subsequent outcome in terms of clinical condition on discharge from the ward is shown also and it may be seen that correspondence between good and intermediate groups became poorer at this later stage.

Some examples of ICPWF power spectra obtained for patients from good (A), intermediate (B) and poor (C) groups are shown in figure 4. These demonstrate typical variations in spectral harmonics occurring between groups.

Simple spectral parameters derived solely from the ICPWF spectra, and relative indices derived from both ICPWF and APWF spectra are shown for the three groups in table II. Mean ICP and CPP values for the respective groups are included also. It may be seen that, while all indices produced significant differences between poor and intermediate groups, only the relative spectral indices differentiated between good and intermediate patients.

Correlations between harmonic count ratio (Nc:Na) and MICP and CPP were poor ($r = 0.27$, $P < 0.01$ and $r = 0.20$, $P < 0.05$, respectively).

The ICPWF/APWF harmonic transfer function obtained from the patients in the good group

TABLE I. *Grouping of 32 head injury patients according to Glasgow Coma Score (GCS) on admission to hospital, clinical condition on discharge from the Intensive Care Unit (ICU) and clinical condition on discharge from the ward, as defined according to a modified Glasgow Outcome Scale · good = potentially employable; intermediate = moderate or severe disability; poor = vegetative state or died during admission*

| | Good | Intermediate | Poor |
|---|---|---|---|
| Admission GCS | 7 | 16 | 9 |
| GCS on discharge from ICU | 6 | 15 | 11 |
| Condition on discharge from ward | 11 | 10 | 11 |

TABLE II. *Intracranial pressure waveform (ICPWF) spectral indices* (SD), *mean intracranial pressure (MICP) and mean cerebral perfusion pressure (CPP) for good, intermediate and poor groups of head injury patients.* n = *Number of patients in group.* **Significant difference* ($P < 0.05$) *from both other groups*

| | Good ($n = 6$) | Intermediate ($n = 14$) | Poor ($n = 10$) |
|---|---|---|---|
| CPP | 78.2 (16.0) | 65.7 (13.1) | 15.3 (36.4)* |
| MICP | 13.0 (6.2) | 16.5 (7.5) | 46.4 (20.2)* |
| ICPWF spectral indices | | | |
| Nc | 11.9 (1.7) | 9.9 (2.2) | 7.8 (1.8)* |
| F90c | 12.6 (1.7) | 11.6 (3.2) | 7.8 (1.8)* |
| HFCc | 8.0 (1.0) | 7.2 (0.7) | 6.6 (0.8)* |
| ICPWF/APWF normalized indices | | | |
| Nc:Na | 1.31 (0.29)* | 0.97 (0.11)* | 0.66 (0.15)* |
| F90c:F90a | 1.36 (0.19)* | 0.95 (0.18)* | 0.64 (0.14)* |
| HFCc.HFCa | 1.41 (0.24)* | 0.98 (0.12)* | 0.68 (0.13)* |

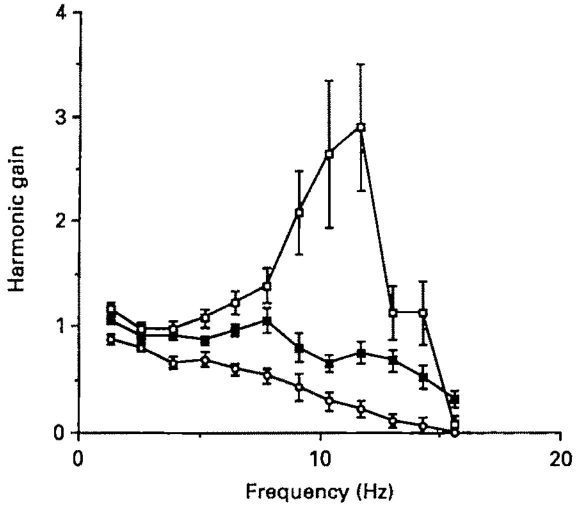

FIG. 5. Effect of increasing severity of injury on transfer function in good (□), intermediate (■) and poor (○) patient groups.

demonstrated a peak in response at frequencies between 10 and 12 Hz (fig. 5). Transfer functions for the intermediate and poor outcome groups indicate that deteriorating clinical status appeared to produce an increasing attenuation of the peaked response observed in the good patient group (fig. 5).

## DISCUSSION

In this study, the patients were grouped according to clinical status in order to highlight spectral differences of clinical significance. Assessment of the patients has been performed before data recording (GCS on admission to hospital) and after recording was completed (GCS on discharge from ICU). In this way, we have tried to ensure that intracranial conditions retained a significant degree of consistency over the period of data collection.

### *Simple spectral parameters*

Differentiating between the poor group patients and the remainder was effective with all indices, both spectrally and physiologically derived (CPP and ICP). This is of limited practical use because, even on clinical grounds, this does not often present a problem. However, differentiating between intermediate and good groups may be a clinical problem, particularly when patients are sedated and sometimes receiving neuromuscular blockers. It is often this intermediate group of patients in whom acute or sub-acute changes in intracranial conditions may occur, and in whom it is most desirable to detect such changes as early as possible.

The simple indices of Nc, HFCc, F90c, CPP and MICP provided non-significant differences between good and intermediate groups. However, the normalized indices (HFCc:HFCa, F90c:F90a and Nc:Na) derived from both ICPWF and APWF spectra did appear to be sensitive enough to distinguish between these groups. Thus normalization of spectral indices would appear to enhance their performance. Nc:Na was obtainable by simple inspection of the respective power spectra, whereas HFCc:HFCa and F90c:F90a required computation of areas under the spectral curves.

*Transfer functions*

Although the physiological and mechanical factors contributing to the transfer functions may be outlined (fig. 4), the relative importance of each component remains unknown. Thus interpretation of transfer function changes would be aided by further knowledge of how the pressure pulsations in the CSF originate. This question has been investigated by previous workers [9, 10]. The most attractive concept is that these waves are generated by the cerebral vessels and transmitted to the CSF spaces via the cerebral parenchyma and other tissues [11]. A further question arising is the relative contributions of arterial and venous vessels [12], although there is evidence to suggest that the ICPWF possesses components from both types of vessels [13]. In addition, because radial arterial pressure signals were used in these patients, the peripheral systemic vasculature also affects transfer function.

The mean transfer function obtained for patients in the good group (fig. 5) agrees with the general configuration obtained for the continuous extradural–carotid arterial transfer function derived for dogs with normal ICP [8]. As in the normal animal model, a peak is obtained (10–12 Hz) which is attributable to resonance in the response of the intracranial cavity.

Comparing this transfer function with those obtained in the intermediate and poor groups, significant changes may be noted with deteriorating clinical condition. Most prominently, there is increasing attenuation of the peak in the transfer function with increasing severity of injury. If these transfer functions are compared with the theoretical response of a simple damped mechanical oscillator (fig. 6), it may be seen that the effect of worsening clinical condition is analogous to increasing the mechanical damping in the second order system. In terms of intracranial contents, the mechanical damping or resistive factors represent the viscous and resistive tissue effects in cerebral parenchyma and vessel walls. Thus changes in these resistive factors may herald acute deterioration in intracranial conditions. This contrasts with the concept that intracranial compliance (or its reciprocal, elastance) is the most useful mechanical index clinically.

The application of transfer function monitoring in detecting acute changes in a patient's intracranial status would be particularly desirable in the intermediate group of patients, in whom the clinical course is most likely to change or be affected by therapeutic intervention (table I). An indication of potential performance was obtained from the records of selected patients from the intermediate outcome group, who were noted to improve during their ICU admission from GCS 6–7 on admission to 9–11 on discharge, and whose transfer functions also "improved" correspondingly. Serial transfer functions plotted on days 1, 3 and 8, for one such patient are shown in figure 7. However, further work is required to establish

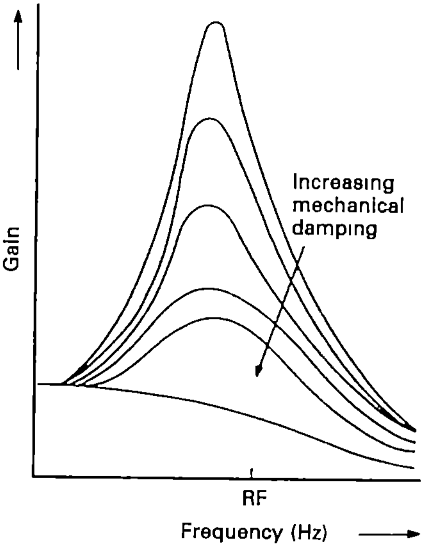

FIG. 6. Response curves for a damped mechanical oscillator.

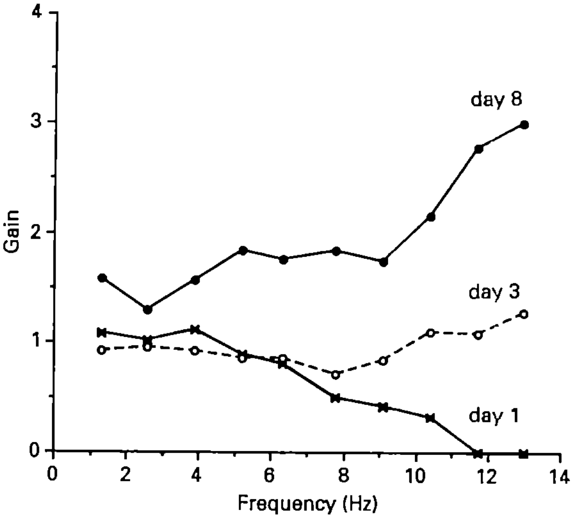

FIG. 7. Serial transfer functions recorded from a patient in the intermediate group, showing an improving clinical course.

if the response of transfer functions is consistent and rapid enough to be clinically useful in detecting acute changes in intracranial conditions.

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# DIFFERENTIAL EFFECTS OF PROPOFOL AND NITROUS OXIDE ON POSTERIOR TIBIAL NERVE SOMATOSENSORY CORTICAL EVOKED POTENTIALS DURING ALFENTANIL ANAESTHESIA

C. J. KALKMAN, H. TRAAST, W. W. A. ZUURMOND AND J. G. BOVILL

## SUMMARY

*We have studied differential effects of propofol and nitrous oxide on posterior tibial nerve somatosensory evoked potentials (PTN-SEP) during a continuous infusion of alfentanil. In study 1, 14 patients received initially 66% nitrous oxide in oxygen, which was replaced 90 min after incision by propofol 6 mg kg$^{-1}$ h$^{-1}$. This substitution resulted in a significant increase in mean P1N1 amplitude from 1.01 (SD 1.14) µV to 2.61 (2.17) µV ($P < 0.01$), while amplitudes of later peaks were unaffected. Latencies of peaks N1, P2 and N2 increased after the substitution. In study 2, 30 patients undergoing spinal surgery received either alfentanil–nitrous oxide anaesthesia (group I, n = 15) or alfentanil–propofol anaesthesia (group II, n = 15). P1N1 amplitude was significantly greater in group II (3.24 (1.08) µV) than in group I (1.64 (0.97) µV) ($P < 0.01$). Latencies of peaks P2 and N2 were of significantly greater duration in group II than in group I. Because early cortical PTN-SEP peaks were preserved better during alfentanil–propofol anaesthesia we conclude that this combination may be a suitable alternative to alfentanil–nitrous oxide anaesthesia, when spinal cord function monitoring with PTN-SEP is indicated.*

***KEY WORDS***

*Anaesthetics, gases: nitrous oxide. Anaesthetics, intravenous: propofol. Analgesics: alfentanil. Brain: evoked potentials.*

Sensory evoked potentials (SEP) are used frequently to monitor specific neural pathways that are at risk during surgery. Posterior tibial nerve somatosensory evoked potentials (PTN-SEP) are used widely to monitor the integrity of the spinal cord during operations in which there is a risk of paraplegia, for example scoliosis surgery and operations involving the thoracic aorta [1, 2]. Changes in latency and amplitude of primary peaks in the SEP waveform may indicate impaired conduction in the pathway monitored. For operations in which SEP monitoring is indicated, the chosen anaesthetic technique should result in the least possible effect on amplitudes and latencies. Opioids have little effect on SEP [3]. The combination of nitrous oxide and a continuous infusion of an opioid is an accepted anaesthetic technique for operations in which spinal cord function monitoring is indicated [4]. Nitrous oxide is a moderate depressant of SEP amplitude, without effects on latency [5].

Propofol has a short duration of action and is ideally suited for total i.v. anaesthesia in combination with an opioid [6]. Because of the rapid recovery after propofol, it could be ideal for orthopaedic operations on the spine, where clinical evaluation of motor function during operation (wake-up test) or in the early postoperative period is important. We have therefore compared the relative effects of nitrous oxide and propofol on intraoperative PTN-SEP in combination with a continuous infusion of alfentanil, in two separate studies.

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TABLE I. *Patient characteristics (mean (range or SD))*

| | Study 1 | Study 2 | |
|---|---|---|---|
| | N$_2$O, propofol | N$_2$O (group I) | Propofol (group II) |
| N | 14 | 15 | 15 |
| Age (yr) | 32.1 (18–45) | 27.7 (18–43) | 26.4 (19–32) |
| Weight (kg) | 70.6 (17.0) | 66.5 (11.8) | 64.9 (11.1) |
| Height (cm) | 173.6 (10.0) | 171.8 (10.3) | 173.9 (8.9) |
| Sex (M/F) | 7/7 | 6/9 | 5/10 |
| Surgical procedure | | | |
| Scoliosis | — | 13 | 12 |
| Vertebral fracture | — | 2 | 3 |

## PATIENTS AND METHODS

### *Study 1*

A crossover design was used to study the effect on PTN-SEP of substituting nitrous oxide with propofol during continuous infusion of alfentanil. We studied 14 patients, ASA physical status I, aged 18–45 yr, undergoing elective procedures lasting more than 2–3 h in which minimal surgical trauma and blood loss were expected, for example dental surgery. All patients gave informed consent to participate in the study which was approved by the local Medical Ethics Committee. None of the patients was taking any drug known to affect SEP.

Patients received diazepam 10 mg orally 1 h before surgery. Anaesthesia was induced with thiopentone 3 mg kg$^{-1}$ and a loading dose of alfentanil 100 µg kg$^{-1}$ given over 10 min. Neuromuscular block was achieved with pancuronium 0.1 mg kg$^{-1}$. Anaesthesia was maintained with 66% nitrous oxide in oxygen and an infusion of alfentanil 2 µg kg$^{-1}$ min$^{-1}$ for the first 90 min of the procedure. Nitrous oxide was discontinued and an infusion of propofol, designed to achieve a steady state plasma concentration of 3.0 µg ml$^{-1}$, was started [7]. Following the loading dose of 1 mg kg$^{-1}$, propofol was administered at a rate of 10 mg kg$^{-1}$ h$^{-1}$ for 10 min, 8 mg kg$^{-1}$ h$^{-1}$ for the next 10 min and 6 mg kg$^{-1}$ h$^{-1}$ thereafter.

### *Study 2*

This study involved 30 patients undergoing spinal surgery for correction of scoliosis or stabilization of vertebral fractures. Patients were allocated randomly to receive either alfentanil–nitrous oxide anaesthesia (group I) or total i.v. anaesthesia with alfentanil–propofol (group II). Patients were aged 18–43 yr, ASA physical status I, and gave informed consent to participate in the study which was approved by the local Medical Ethics Committee. None of the patients were taking any drug known to affect SEP. Patients received diazepam 10 mg orally 1 h before surgery.

In group I, anaesthesia was induced as described for study 1. Pancuronium 0.1 mg kg$^{-1}$ was given to provide neuromuscular block. Anaesthesia was maintained with 66% nitrous oxide in oxygen and an infusion of alfentanil 2 µg kg$^{-1}$ min$^{-1}$.

In group II, anaesthesia was induced with propofol 1 mg kg$^{-1}$ and a loading dose of alfentanil 100 µg kg$^{-1}$ given over 10 min. Pancuronium 0.1 mg kg$^{-1}$ was given to provide neuromuscular block. The lungs of the patient were ventilated with 33% oxygen in air. A continuous infusion of alfentanil 2 µg kg$^{-1}$ min$^{-1}$ was given until 30 min before the end of surgery. Following the loading dose, propofol was administered at a rate of 10 mg kg$^{-1}$ h$^{-1}$ for 10 min, 8 mg kg$^{-1}$ h$^{-1}$ for the next 10 min and 6 mg kg$^{-1}$ h$^{-1}$ thereafter. In both groups, additional doses of pancuronium were given if needed. If controlled hypotension was required, sodium nitroprusside and labetalol were given to maintain mean arterial pressure at 60–70 mm Hg throughout the procedure. Ventilation was adjusted to maintain the end-tidal partial pressure of carbon dioxide ($P\text{E}'_{CO_2}$) at 4.5–5.5 kPa. Heated humidified gases, a warming mattress and i.v. fluid warmers were used to prevent hypothermia in all patients.

All patients stayed in the recovery room for 24 h and were questioned the next day for recall of intraoperative or anaesthetic events.

### *Somatosensory evoked potentials recording*

A Nicolet Pathfinder II system was used for stimulation and recording. Both posterior tibial nerves were stimulated at the ankle via subdermal needle electrodes using constant current square wave pulses of 200 µs duration. The stimulus intensity was twice the motor threshold. Somatosensory evoked potentials were recorded from the scalp (Cz–Fpz) using silver–silver chloride disc electrodes. Electrode impedance was maintained less than 2 kΩ. The EEG signal was amplified 50000 times and filtered between 5 and 250 Hz (−3dB). For each waveform, 360 sweeps were averaged. Averages were made with 512 datapoints on a time base of 200 ms, giving a latency resolution of 0.4 ms. In all groups, PTN-SEP were acquired continuously starting 30 min after induction of anaesthesia. The continuous acquisition of SEP waveforms was controlled by a computer program which automatically stored the waveforms on hard-disk, together with the values of mean arterial pressure, $P\text{E}'_{CO_2}$ and nasopharyngeal temperature derived from the patient monitor (HP 3854A). Acquisition was halted automatically during diathermy.

In eight patients in group II we studied the effects of induction of anaesthesia with alfentanil and propofol on PTN-SEP. During this phase the stimulus current was limited to the motor threshold.

For each waveform, the latencies and peak-to-peak amplitudes of the primary cortical peaks P1 to N2 were identified using on-screen cursors. Data were analysed with analysis of variance of repeated measurements (BMDP program 2V). Where appropriate, comparisons were made using paired and unpaired *t* tests with Bonferroni correction for multiple comparisons. Results are expressed as mean (SD).

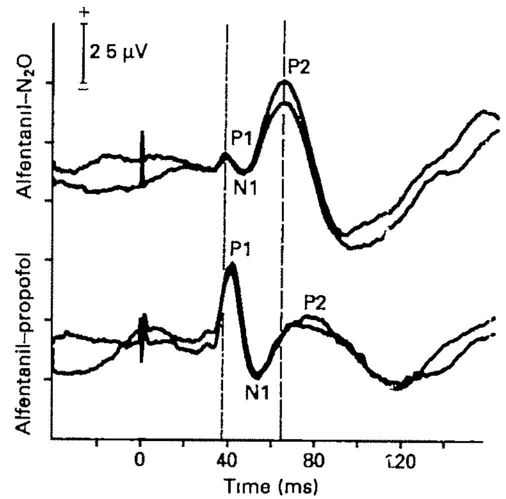

FIG. 1. Posterior tibial nerve somatosensory evoked potentials from one patient during alfentanil–nitrous oxide anaesthesia and 15 min after substitution of nitrous oxide with propofol. P1 = first positive cortical peak; N1 = first negative cortical peak; P2 = second positive cortical peak.

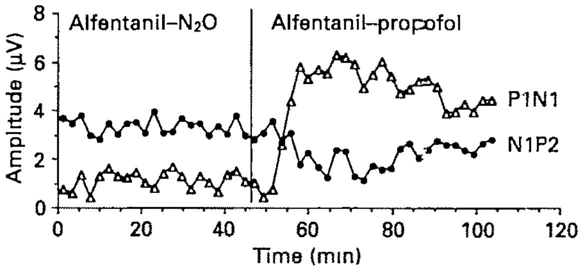

FIG. 2. Peak-to-peak PTN-SEP amplitudes P1N1 and N1P2 *vs* time from one patient recorded during alfentanil–nitrous oxide anaesthesia and after substitution of nitrous oxide with propofol.

## RESULTS

There were no significant differences in age, gender, weight, height or type of operation between the two groups in study 2 (table I). None of the patients in study 2 had neurological abnormalities or radiological evidence of spinal cord compression. No patient was able to recall any event during surgery or anaesthesia. In study 1, the average decrease in nasopharyngeal temperature was 0.2 (0.39) °C; in study 2 the average temperature decreased 0.6 (0.46) °C in group I and 0.7 (0.49) °C in group II. Controlled hypotension was used in three patients in both groups. Within the two groups there was no correlation between mean arterial pressure and any of the PTN-SEP parameters. None of the patients in study 2 had deterioration or loss of PTN-SEP during surgery. There were no postoperative neurological complications.

### *Study 1*

Figure 1 shows PTN-SEP waveforms from one patient during alfentanil–nitrous oxide anaesthesia and after substitution of nitrous oxide by propofol. In this patient P1N1 amplitude increased from 0.65 µV during nitrous oxide to 4.42 µV during the propofol infusion. The changes in amplitude with time for the same patient are shown in figure 2. The effect of substitution of nitrous oxide by propofol is apparent within

TABLE II. *Latencies and amplitudes of PTN-SEP (mean (SD)) during anaesthesia with alfentanil–nitrous oxide and after substitution of nitrous oxide with propofol (Study 1, n = 14). *$P < 0.05$, **$P < 0.01$, compared with nitrous oxide*

| | $N_2O$ | Propofol +15 min | Propofol +30 min |
|---|---|---|---|
| Latency (ms) | | | |
| P1 | 41.8 (3.93) | 42.7 (3.64) | 42.5 (3.62) |
| N1 | 49.8 (5.04) | 52.3 (3.96)* | 52.1 (4.22)* |
| P2 | 65.3 (4.33) | 69.2 (5.82)* | 69.8 (5.28)* |
| N2 | 92.1 (10.26) | 102.6 (8.56)** | 108.3 (6.15)** |
| Amplitude (μV) | | | |
| P1N1 | 1.01 (1.14) | 2.61 (2.17)** | 2.71 (2.01)** |
| N1P2 | 2.24 (1.35) | 2.14 (1.08) | 2.37 (0.91) |
| P2N2 | 4.81 (2.81) | 3.79 (1.86) | 4.29 (2.36) |

TABLE III. *PTN-SEP latencies and amplitudes (mean (SD)) before and 5 min after induction of anaesthesia with propofol and alfentanil (n = 8). **$P < 0.01$ compared with before induction*

| | Before induction | After induction |
|---|---|---|
| Latency (ms) | | |
| P1 | 42.1 (3.36) | 40.9 (3.65) |
| N1 | 51.2 (3.76) | 49.7 (5.71) |
| P2 | 63.7 (3.74) | 65.6 (7.99) |
| N2 | 79.0 (4.59) | 98.6 (16.15)** |
| Amplitude (μV) | | |
| P1N1 | 4.43 (1.96) | 3.36 (1.69) |
| N1P2 | 4.58 (1.90) | 4.31 (2.42) |
| P2N2 | 5.20 (2.74) | 6.43 (2.99) |

2.5 min—the time needed for the acquisition of one PTN-SEP waveform.

Average values of PTN-SEP latencies and amplitudes during alfentanil–nitrous oxide anaesthesia and 15 min and 30 min after discontinuation of nitrous oxide and the start of the propofol infusion are given in table II. Substitution of nitrous oxide by propofol resulted in significant increases in latency of the N1, P2 and N2 peaks and a highly significant increase in the peak-to-peak amplitude of P1N1. The amplitudes of N1P2 and P2N2 did not change. There were no significant differences in latencies and amplitudes between the waveforms obtained 15 and 30 min after starting the propofol infusion.

*Study 2*

Induction of anaesthesia with propofol and alfentanil in eight patients in group II resulted in a significant prolongation of N2 peak latency (table III). The latencies of peaks P1, N1 and P2 did not change. There were no changes in the amplitudes of any peaks. Table IV summarizes the latencies and amplitudes in groups I and II during operation, at 30 min and 90 min after incision. In the patients undergoing scoliosis correction, the PTN-SEP at 90 min were acquired before the final distraction was applied. P2 and N2 latencies were of significantly greater duration in group II compared with group I. P1N1 amplitude was significantly greater in group II than in group I. N1P2 and P2N2 amplitudes were not significantly different between the groups. There was a small but statistically significant increase in the latency of peaks P1 and N1 at 90 min compared with 30 min in group II.

## DISCUSSION

The recording during operation of reproducible SEP is possibly only when anaesthesia does not result in depression of amplitudes to such a degree that peak identification becomes impossible. All inhalation anaesthetic agents cause a marked, dose-related depression of cortical SEP amplitude [8]. Nitrous oxide does not influence latencies, but depresses SEP amplitudes by about 50% of control values [5]. Continuous infusions of an opioid with nitrous oxide have been advocated as the optimum anaesthetic technique, giving minimal depression of SEP amplitudes [4]. Alfentanil has only minor effects on PTN-SEP. Given in large doses for cardiac surgery, it did not increase latencies of early cortical PTN-SEP. Amplitudes decreased to 60% of the awake value 1 h after induction [3].

Our study indicated that propofol caused less

TABLE IV. *PTN-SEP latencies and amplitudes 30 min and 90 min after skin incision, during alfentanil–nitrous oxide anaesthesia (group I) or alfentanil–propofol anaesthesia (group II) (mean (SD)).* *$P < 0.05$, **$P < 0.01$, *compared with N$_2$O;* †$P < 0.05$ *compared with 30 min*

| | Group I: N$_2$O | | Group II: propofol | |
|---|---|---|---|---|
| | 30 min | 90 min | 30 min | 90 min |
| Latency (ms) | | | | |
| P1 | 42.1 (2.93) | 42.3 (2.49) | 42.7 (2.93) | 43.8 (3.32)† |
| N1 | 51.0 (3.67) | 51.1 (3.80) | 53.0 (3.92) | 54.5 (4.23)† |
| P2 | 69.7 (8.49) | 68.5 (4.69) | 72.1 (4.77)* | 74.3 (5.69)* |
| N2 | 94.7 (8.57) | 94.0 (8.23) | 109.9 (6.35)** | 109.0 (9.40)** |
| Amplitude (μV) | | | | |
| P1N1 | 1.64 (0.97) | 1.65 (0.98) | 3.24 (1.08)** | 3.17 (1.74)** |
| N1P2 | 3.48 (1.60) | 3.37 (1.30) | 3.37 (1.58) | 2.82 (1.54) |
| P2N2 | 5.69 (1.63) | 5.62 (1.41) | 5.14 (2.46) | 4.21 (2.43) |

depression of PTN-SEP amplitude than nitrous oxide. Maurette and colleagues [9] evaluated the effects of propofol on PTN-SEP during spinal surgery. They induced anaesthesia with propofol 2 mg kg$^{-1}$, followed by an infusion of propofol 6 mg kg$^{-1}$ h$^{-1}$. The lungs of the patients were ventilated with 50% nitrous oxide in oxygen. Intermittent bolus doses of dextromoramide were given according to clinical requirements. No change in the latency of the P40 peak (equivalent to P1 in our study) was observed, but there was a significant, 66% decrease in amplitude, which the authors attributed to the effect of propofol. They concluded that propofol is an unsatisfactory anaesthetic drug when monitoring of spinal cord function with PTN-SEP is indicated. However, the combined effects of nitrous oxide and propofol may have been responsible for the observed decrease in amplitude. Because no attempts were made to separate the effects of nitrous oxide and propofol, it is difficult to compare their results with our findings.

Consistent decreases in PTN-SEP amplitude were observed when 50% nitrous oxide was introduced during a fentanyl–oxygen technique, but nitrous oxide had no effect on latency [5]. Inhalation of increasing concentrations of nitrous oxide in awake volunteers showed that SEP amplitude depression by nitrous oxide is dose-related and involved all cortical peaks of PTN-SEP [10]. In the patients in study 1, substitution of nitrous oxide by propofol altered the overall shape of the PTN-SEP waveform in favour of the first cortical peak, which is thought to reflect arrival of the impulse at the sensory cortex [11]. This more than twofold increase in P1N1 amplitude, and the difference in P1N1 amplitude between groups I and II in study 2, may indicate that nitrous oxide depresses the early cortical peaks more than later peaks.

Induction of anaesthesia with propofol has been reported to cause a marked increase in latency of median nerve SEP (MN-SEP) peaks with latencies greater than 25 ms, whereas those with latencies less than 20 ms were unaffected [12, 13]. No significant decrease in the amplitude of the N20–P25 complex was observed in these studies, but peaks with latencies greater than 25 ms were either absent or their amplitude was severely depressed. A temporary increase in N20–P25 amplitude (the first cortical peak of MN-SEP) was observed in five of 10 patients after induction with propofol [14]. In our study, induction of anaesthesia with propofol given in combination with alfentanil had no effect on PTN-SEP amplitudes and no effect on the latencies of earlier cortical peaks.

One possible explanation for the greater P1N1 amplitude observed in our alfentanil–propofol group could be that the depth of anaesthesia in patients in this group was less adequate than in the alfentanil–nitrous oxide group. The propofol infusion scheme used in our study was designed to achieve a blood concentration of propofol of about 3.0 μg ml$^{-1}$ [7]. In their study, Roberts and colleagues [7] then used this infusion scheme in combination with nitrous oxide and fentanyl 3 μg kg$^{-1}$ to provide anaesthesia for patients undergoing superficial body surgery. In our study, we combined propofol with alfentanil but without nitrous oxide. It is possible that, in individual patients, the propofol and alfentanil concentrations might have been less than sufficient for optimal levels of anaesthesia. However, none of our patients reported any recall of intraoperative events when questioned 24 h after surgery.

Haemodynamic changes such as hypertension or tachycardia in response to surgical stimuli are generally considered an indication of inadequate anaesthesia. Three patients in each of our groups received sodium nitroprusside for controlled hypotension at the request of the surgeon. None of the other patients, who did not receive sodium nitroprusside, exhibited haemodynamic or autonomic changes indicative of inadequate anaesthesia. Richards and colleagues [15] carried out a dose-finding study of different propofol infusion regimens in combination with a continuous infusion of alfentanil $50\ \mu g\ kg^{-1}\ h^{-1}$. The $ED_{95}$ for the motor response to skin incision was $5\ mg\ kg^{-1}\ h^{-1}$ (95% confidence limits $4.13–8.8\ mg\ kg^{-1}\ h^{-1}$). No patient in the group receiving the 10:8:6 infusion scheme moved on surgical stimulation. In our study, the alfentanil infusion rate of $2\ \mu g\ kg^{-1}\ min^{-1}$ was twice that used in the study by Richards' group. This makes it highly unlikely that the increased SEP amplitude observed during alfentanil–propofol total i.v. anaesthesia in our study was caused by light propofol anaesthesia.

In awake patients, the stimulus current delivered to the posterior tibial nerves is limited by patient tolerance. For this reason, we limited the stimulus current for the pre- and post-induction recordings to the motor threshold. For subsequent recordings, the stimulus current was increased to twice the motor threshold to ensure a maximal evoked response for spinal cord monitoring. Because PTN-SEP amplitude is dependent on stimulus current, we were not able to compare PTN-SEP recorded before and immediately after induction of anaesthesia with those obtained during operation.

Prevention of hypothermia during spinal surgery is difficult, because of the large wound area and the positioning of the patient which limits contact with the warming mattress. Despite preventive measures including the use of a warming mattress, heated humidified gases and warmed infusion fluids, the average temperature decrease during spinal surgery in our patients was 0.6–0.7 °C. In an earlier study we reported that P1 latency of PTN-SEP increased by 1 ms per °C decrease in nasopharyngeal temperature [14]. This could explain partly the observed latency increase at 90 min after skin incision compared with 30 min after skin incision in group II.

In conclusion, propofol given in combination with alfentanil has less effect on early cortical PTN-SEP peaks than nitrous oxide in combination with alfentanil. The use of propofol allows better identification of the primary cortical peaks which are used to monitor spinal cord function during surgery. Total i.v. anaesthesia with propofol and alfentanil is a satisfactory anaesthetic technique when intraoperative monitoring of PTN-SEP is indicated.

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# BRAIN AND SPINAL CORD METABOLIC ACTIVITY DURING PROPOFOL ANAESTHESIA

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## SUMMARY

*We have investigated the effects of propofol anaesthesia on the metabolic activity pattern of 35 regions of the rat brain and cervical spinal cord using the $^{14}C$-2-deoxyglucose technique. Anaesthesia was produced by an i.v. bolus of the commercial preparation of the drug (8 mg $kg^{-1}$) and maintained with successive bolus administrations of 6 mg $kg^{-1}$. Functional activity values (expressed as rates of local utilization of glucose) were reduced in 31 grey matter and two white matter structures in a propofol group relative both to saline-injected and vehicle-injected (aqueous emulsion containing 10% soya bean oil, 1.2% egg phosphatide and 2.25% glycerol) controls. Values from the two control groups did not differ significantly. Propofol-induced depression of metabolic activity was present in central nervous system regions belonging to sensory (auditory, visual and somatosensory), motor and limbic systems, including spinal cord grey matter. Mean percentage decreases ranged from 40% (vestibular nuclei) to 76% (cingulate cortex). Although these values may be slightly overestimated because of the modest increase in $Pa_{CO_2}$ in the anaesthetized group, propofol appeared to elicit generalized reduction of central nervous system functional activity.*

**KEY WORDS**

*Anaesthetics, intravenous · propofol Brain. glucose metabolism. Metabolism · brain, spinal cord.*

Propofol (Diprivan), a short-acting i.v. general anaesthetic [1], has been utilized in neurosurgery and for sedation of patients in intensive care units [2, 3]. Clinical studies have shown that cerebral blood flow, oxygen consumption and intracranial pressure are reduced during propofol anaesthesia [4–7]. However, metabolic or blood flow studies in humans are limited by the spatial resolution of the techniques used, which usually yield mean values from large portions of the brain. This is of particular relevance for investigations concerning general anaesthetics, some of which may induce heterogenous effects in different central nervous system (CNS) regions [8–10]. Furthermore, despite its obvious clinical relevance, little information is available on anaesthetic effects on spinal cord functional activity. Using the spatial resolution offered by the autoradiographic carbon-14-labelled 2-deoxyglucose (2DG) method [11], in the present study we have investigated the metabolic activity of 35 brain and spinal cord structures under propofol anaesthesia in the rat.

A preliminary communication was presented at the XLIII Annual Meeting of the Italian Anaesthesiological Society [12].

## MATERIALS AND METHODS

Investigations were carried out in male Sprague–Dawley rats weighing 250–300 g (Morini, S. Polo d'Enza, Italy). The animals were anaesthetized with pentobarbitone and polyethylene catheters (PE-50, Becton Dickinson) were inserted into the right external jugular vein and common carotid artery, and exteriorized at the back of the neck. Two days later, the animals were allocated randomly to propofol or control groups. Rats of the former group ($n = 6$) received an i.v. bolus of propofol 8 mg $kg^{-1}$ from the commercial preparation (Diprivan, ICI Pharma). Anaesthesia (as

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defined by loss of the righting reflex) was maintained by successive bolus injections of 6 mg $kg^{-1}$, performed at the first detectable movement of the animal. The total dose of propofol was 38 mg $kg^{-1}$ for each rat, divided in six administrations. Intervals between injections varied from 6 to 10 min and usually increased with time. This regimen was chosen on the basis of preliminary experiments in order to maintain mean systemic arterial pressure (which was continuously monitored throughout the experiments) greater than 80 mm Hg. The effective anaesthetic doses are about three times greater in rats than in humans. Blood concentrations of drug were not measured. Pharmacokinetic profiles are similar in different species; on the basis of the administration schedule adopted, it is likely that after an initial peak of 12–15 µg $ml^{-1}$ (before the $^{14}$C-2DG experiment), blood concentrations of propofol fluctuated at more than 3 µg $ml^{-1}$ [13, 14].

During anaesthesia, rats were spontaneously breathing in the prone position on a cotton pad. Rectal temperature was monitored and maintained at 36.5–37 °C by an infra-red lamp. Control rats received an equivalent amount of vehicle (aqueous emulsion containing 10% w/v soya bean oil, 1.2% w/v egg phosphatide and 2.25% w/v glycerol, $n = 4$) or saline ($n = 6$) i.v., administered according to a similar schedule. Ten minutes after the first propofol or control injection, an i.v. bolus of $^{14}$C-2DG (100 µCi $kg^{-1}$, Amersham, in 0.3 ml of saline) was given; studies were then performed as described by Sokoloff and colleagues [11]. Briefly, 12–13 timed arterial blood samples (80–100 µl each) were drawn during the 45-min period of investigation in order to follow the time course of plasma concentrations of glucose (Beckman Glucose Analyzer 2) and $^{14}$C-2DG (Packard TRI-CARB 460 C). Control animals were free to move around in their cages, although they usually sat quietly in a corner. Immediately before and 25 min after the injection of $^{14}$C-2DG, larger arterial blood samples (0.2 ml) were withdrawn in order to measure pH, $Pa_{CO_2}$ and $Pa_{O_2}$ (IL gas analyser 213).

Forty-five minutes after the injection of $^{14}$C-2DG, animals were killed by an overdose of pentobarbitone i.v. Brain and spinal cord were removed rapidly, frozen in freon chilled to −80 °C and stored at −80 °C. Serial coronal sections were later obtained by cryostat at −20 °C, dried on a hot plate at 60 °C and processed for autoradiography. Calibrated methylmethacrylate standards were exposed together with sections in x-ray cassettes in order to allow measurement of the isotope uptake. Autoradiographs (Hyperfilm Betamax, Amersham) were analysed quantitatively with the aid of programs developed on a computerized image processing system [15]. Measurements were obtained from at least four sections for each region of interest. Mean local glucose utilization (LGU) rates were calculated according to the procedure described [11] from 32 grey matter and three white matter regions of the brain and cervical enlargement of the spinal cord. Values from the left and right sides of the CNS were not significantly different in any group; therefore, they were pooled for subsequent analyses. One-way analysis of variance (ANOVA) was used to ascertain between-group differences, with Bonferroni's correction for the number of comparisons. A corrected value of $P < 0.05$ was assumed to be significant.

TABLE I. *Physiological variables (mean (SEM)). *Significantly different from control groups (P < 0.05)*

| | Saline ($n = 6$) | Vehicle ($n = 4$) | Propofol ($n = 6$) |
|---|---|---|---|
| $Pa_{O_2}$ (kPa) | 13.03 (0.53) | 12.50 (0.40) | 10.92 (0.45)* |
| $Pa_{CO_2}$ (kPa) | 4.98 (0.22) | 5.09 (0.18) | 6.01 (0.28)* |
| pH | 7.42 (0.02) | 7.39 (0 009) | 7.37 (0.001) |
| MAP (mm Hg) | 110 (8) | 109 (4) | 96 (4) |
| Glucose (mmol $litre^{-1}$) | 7.48 (0.34) | 7.9 (0.72) | 6.94 (0.41) |

## RESULTS

Mean physiological values during the course of the experiments are shown in table I.

In all animals propofol injections caused a mild decrease (about 15 mm Hg) in mean arterial pressure (MAP) within a few seconds. Subsequently, a stable baseline could usually be observed, except for an increase towards pre-injection values beginning about 60 s before the appearance of the first detectable head or body movements. In all rats, MAP values were greater than 80 mm Hg throughout the experiment. A small but significant increase in $Pa_{CO_2}$ and decrease in $Pa_{O_2}$ occurred in the propofol group.

Plasma concentrations of glucose were in the physiological range and did not differ significantly between groups. Changes from baseline did not exceed 10%.

TABLE II. *Metabolic activity values (mean* (SEM)). *Significant difference from control*: *P < 0.05; **P < 0.01

| | LGU (μmol/100 g min$^{-1}$) | | |
|---|---|---|---|
| | Saline ($n = 6$) | Vehicle ($n = 4$) | Propofol ($n = 6$) |
| Spinal cord | | | |
| Anterior horn | 41 (1) | 46 (3) | 19 (2)** |
| Central grey | 47 (1) | 50 (3) | 18 (1)** |
| Posterior horn | 42 (2) | 44 (2) | 17 (1)** |
| Brainstem and cerebellum | | | |
| Bulbar reticular formation | 48 (4) | 54 (3) | 21 (1)** |
| Vestibular nuclei | 90 (3) | 105 (5) | 58 (5)* |
| Cerebellar nuclei | 78 (4) | 84 (5) | 41 (4)** |
| Cerebellar cortex | 51 (3) | 54 (5) | 21 (2)** |
| Superior olivary complex | 105 (7) | 116 (2) | 88 (8) |
| Inferior colliculus | 112 (5) | 122 (4) | 65 (4)** |
| Superior colliculus | 75 (5) | 74 (6) | 30 (2)** |
| Substantia nigra | 56 (3) | 55 (2) | 25 (1)** |
| Interpeduncular nucleus | 98 (10) | 99 (7) | 48 (2)** |
| Diencephalon | | | |
| Medial geniculate nucleus | 91 (2) | 91 (6) | 37 (1)** |
| Lateral geniculate nucleus | 63 (5) | 67 (3) | 27 (3)** |
| Ventro-basal thalamus | 84 (7) | 80 (10) | 29 (3)** |
| Lateral thalamus | 75 (4) | 88 (9) | 26 (3)** |
| Anterior thalamus | 88 (6) | 106 (11) | 30 (2)** |
| Hypothalamus | 51 (4) | 46 (4) | 21 (3)** |
| Telencephalon | | | |
| Globus pallidus | 46 (2) | 37 (2) | 23 (3)** |
| Caudate nucleus | 85 (4) | 76 (5) | 32 (4)** |
| Septal nuclei | 40 (4) | 43 (5) | 18 (2)** |
| Amygdala | 77 (4) | 66 (3) | 33 (5)** |
| Visual cortex | 80 (2) | 82 (4) | 33 (2)** |
| Auditory cortex | 108 (6) | 101 (8) | 52 (4)** |
| Somatosensory cortex | 85 (6) | 75 (6) | 32 (4)** |
| Parietal cortex | 87 (7) | 78 (5) | 37 (3)** |
| Frontal cortex | 80 (3) | 78 (4) | 30 (4)** |
| Cingulate | 92 (7) | 90 (9) | 22 (4)** |
| Entorhinal cortex | 54 (5) | 58 (1) | 31 (4)* |
| Pre-subiculum | 72 (4) | 76 (4) | 28 (3)** |
| Hippocampus (CA1 field) | 62 (4) | 56 (6) | 26 (1)** |
| Dentate gyrus | 51 (4) | 44 (3) | 26 (1)** |
| White matter structures | | | |
| Dorsal column (spinal cord) | 16 (1) | 13 (1) | 7 (1)** |
| Cerebellar white matter | 34 (2) | 33 (1) | 12 (2)** |
| Corpus callosum | 30 (3) | 26 (2) | 16 (2) |

Mean LGU values of 33 structures were significantly lower in the propofol group relative to both saline- and vehicle-injected animals. Values from the two control groups did not differ significantly from each other in any region investigated. Propofol-induced decreases in LGU were found both in the spinal cord and brain. Structures belonging to somatosensory, auditory, visual and motor systems, in addition to limbic circuits, were affected markedly (table II), but only a trend towards a decrease was obtained in the superior olivary complex and corpus callosum.

Mean percentage differences in LGU values of somatosensory and motor structures in the propofol group compared with mean values in controls (saline + vehicle groups, $n = 10$) are shown in figure 1. The degree of propofol-induced depression of metabolic activity was similar in grey matter structures of the spinal cord and brain, and in white matter tracts. The greatest significant percentage decrease in LGU among the 33 structures was found in the cingulate cortex (−76 %), and the least (−40 %) in the vestibular nuclei.

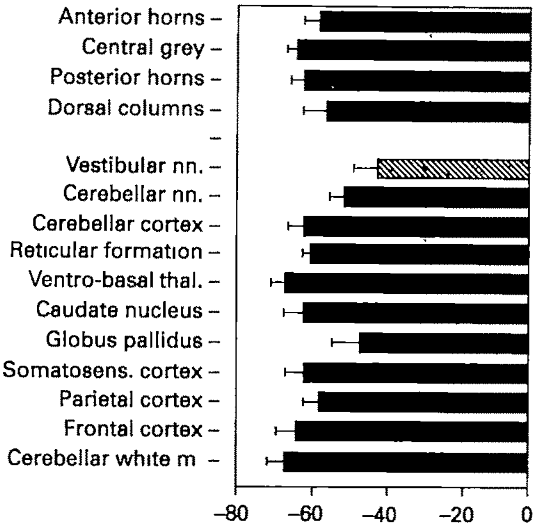

FIG. 1. Mean percentage decreases in LGU (SEM) relative to controls (vehicle- and saline-injected rats, $n = 10$) observed in the propofol group in four regions of the cervical spinal cord (above) and 11 somatosensory and motor brain centres (below). The propofol-induced LGU depression was quantitatively similar in the brain and spinal cord. The drug effect may be slightly overestimated, because of a small increase in $Pa_{CO_2}$ in anaesthetized animals (see Discussion). ■ = $P < 0.05$; ■ = $P < 0.01$.

## DISCUSSION

The results of the present study show that propofol induced a generalized and substantial depression of rates of local utilization of glucose by central nervous system structures in unstimulated rats. This was not caused by the lipid/aqueous emulsion vehicle, which did not modify LGU values.

It should be emphasized that the effect of propofol was probably overestimated, because of the slight increase in $Pa_{CO_2}$ in anaesthetized animals. It is unlikely, however, that this additional factor accounted *per se* for the observed metabolic activity pattern, as greater $Pa_{CO_2}$ values are usually required to alter cerebral oxygen and glucose metabolic rate substantially. For instance, Miller, Hawkins and Veech [16] found a 13% decrease in glucose utilization rates at a $Pa_{CO_2}$ of 10.8 kPa and Van Nimmen and colleagues [17] described a 26% mean decrease in LGU at $Pa_{CO_2}$ 10.7 kPa. In a preliminary study, Des Rosiers and colleagues [18] observed a 35% decrease in LGU at a $Pa_{CO_2}$ of 6.5 kPa. The $Pa_{CO_2}$ values found in the propofol group correspond to an increase of 0.7 kPa (assuming a normal value of 5.3). On the basis of the results of these studies [16–18], it can be calculated that this should not affect LGU by more than 20%.

The $Pa_{CO_2}$ effect could be avoided by performing studies in paralysed animals undergoing artificial ventilation. However, for ethical reasons another general anaesthetic drug would be necessary, thereby invalidating comparison with the awake state.

The $^{14}$C-2-deoxyglucose method has been used extensively in recent years as a tool for monitoring simultaneously the effects of physiological changes or pharmacological interventions on different central nervous system structures [19]. LGU values in the mammalian central nervous system closely reflect the activity of neurones, and particularly of fibre endings [20–22]. In the present study we adopted a slightly modified technique, in which vessels were cannulated 2 days in advance and animals were moving freely during the study period. This offers the advantage of substantially reducing possible interference from surgical preparation and anaesthesia on the one hand, and from restraining procedures on the other [23–25]. The rank order of LGU values in the different CNS structures in control groups, and the range of metabolic activities, are in line with recent results in the rat, from different laboratories [9, 10, 17, 26].

The 2DG method requires steady state conditions during investigations. As discussed in a recent methodological review [27], major persisting changes in the brain physiological state in the first 15 min of the experimental period may obscure the significance of measured LGU values. This does not appear to be the case for the present study, in which behavioural and physiological variables showed minor and transient changes.

The integrated functional activity of CNS structures was depressed uniformly by propofol anaesthesia. The observed metabolic pattern in brain structures is similar to that found under barbiturate anaesthesia [11, 28]. In contrast, other general anaesthetics such as ketamine, halothane and isoflurane were found either not to affect, or even to increase, LGU values in some structures, particularly in motor or limbic systems and at intermediate dosages [8–10, 29, 30]. This does not appear to be the case for propofol; indeed, decreases in LGU found in some limbic regions such as the cingulate cortex and anterior thalamus were among the greatest observed. Metabolic values of sensory structures are usually depressed in a dose-dependent manner by all drugs [8–11, 28–30]. The investigated visual, auditory and somatosensory thalamo–cortical relay and integration centres usually displayed more than 50% reduction in LGU under propofol anaesthesia.

The spinal cord is the first station of the somatosensory system and is thought to play an essential role in processing noxious stimuli [31]. Quantitatively, functional activity depression observed at this level was similar to that found at supraspinal sites; moreover, it was present in both the ventral and dorsal horns. This is in contrast with the effects of pentobarbitone described by Crosby, Crane and Sokoloff, which were restricted to the deep laminae of the dorsal horns and lateral funiculus; nitrous oxide induced a significant increase in LGU in the spinal cord [26].

With few exceptions [32, 33], experimental data on CNS metabolic activity patterns under general anaesthesia have been obtained in unstimulated animals. It will be worthwhile to extend these types of study using selective noxious stimuli, in order to assess the degree of transmission of nociceptive information in the spinal cord and brain in relation to the type and dosage of drug.

On the basis of the metabolic depression found in this study, it appears that propofol elicited a degree of "CNS protection" at both spinal and supraspinal sites. Further experimental studies are required in order to assess if regional cerebral and spinal cord blood flow–metabolic coupling is affected by the drug.

## ACKNOWLEDGEMENTS

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*British Journal of Anaesthesia* 1991; **66**: 496–499

# EFFECT OF KETANSERIN ON INTRAOPERATIVE BLOOD LOSS DURING TOTAL HIP ARTHROPLASTY IN ELDERLY PATIENTS UNDER GENERAL ANAESTHESIA

R. VAN EE AND J. C. VAN OENE

## SUMMARY

*We have studied the effect of ketanserin, a selective serotonin $S_2$-receptor antagonist, on surgical bleeding in a double-blind, placebo-controlled study in elderly patients undergoing total hip arthroplasty. One group of patients (n = 9) received ketanserin 10 mg i.v. followed by an infusion of 0.075 mg $kg^{-1}$ $h^{-1}$. The second group (n = 8) received placebo. Both groups were comparable with regard to age, height and body weight. Mean intraoperative blood loss was 454 ml with ketanserin and 894 ml with placebo (P = 0.004; Wilcoxon two-sample test). Mean duration of the operation was less with ketanserin (112 min) than with placebo (134 min) (P = 0.004), but rate of blood loss was also less with ketanserin (4.1 vs 6.7 ml $min^{-1}$; P = 0.03). In the ketanserin group, mean arterial pressures tended to be less than in the placebo group. Reductions in central venous pressure were similar in both groups. There were no complications in relation to the use of ketanserin.*

**KEY WORDS**

*Age factors Blood loss Serotonin ketanserin Surgery: orthopaedic.*

Total hip arthroplasty (THA) is associated frequently with considerable intraoperative bleeding, necessitating the replacement of circulating volume with blood products. Blood loss may be reduced by induced arterial hypotension and by spinal or extradural anaesthesia [1–7]. The beneficial effect on blood loss is caused probably by arterial and venous dilatation with redistribution of blood flow away from the operation site to dependent parts. Both techniques have disadvantages in the elderly, and other methods of reducing blood loss merit investigation.

Ketanserin is a selective 5-$HT_2$ antagonist that has additional α-blocking effects [8]. It reduces increased arterial pressure with a slight reduction in heart rate [9] and is used currently as an oral antihypertensive drug that is particularly effective in patients older then 60 yr [8,10]. Ketanserin has a vasodilator action on both resistance and capacitance vessels [9,11]. It is likely that, after i.v. ketanserin, there is diversion of blood to skin vessels [12]; it seems to have a haemodynamic effect similar to that induced by regional anaesthesia.

The purpose of this pilot study was to evaluate the feasibility of use of ketanserin as an agent which could contribute to decreased blood loss in THA under general anaesthesia with intermittent positive pressure ventilation (IPPV). As postoperative blood loss seems to be influenced less by the anaesthetic technique [3,13], we have investigated only the effect of ketanserin on intraoperative blood loss.

## PATIENTS AND METHODS

The study was approved by the Institutional Ethics Committee. Written informed consent was obtained from all patients. Exclusion criteria were coagulation disturbances, severe hepatic dysfunction, hypokalaemia (serum potassium $\leqslant$ 3.5 mmol $litre^{-1}$) and concomitant use of vasodilators (such as nitroprusside, nitroglycerin, labetalol, droperidol) or NSAID. Initially, we studied 20 patients aged > 60 yr, ASA I and II. Subsequently, three of these were excluded: one patient because of a previously undetected abnormality in the

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coagulation screen, one who had accidentally received dextran before induction and a third patient in whom a different operation was performed. Thus 17 patients (15 women) with advanced osteoarthritis were investigated during THA under general anaesthesia. Only patients whose hip complaints had led to admission and subsequent operation were included in the study.

Routine preoperative screening included full blood count, electrolytes, chest x-ray and ECG, and revealed no abnormalities. All patients had normal bleeding times, activated coagulation times, prothrombin times and thrombocyte counts. By random selection, patients were assigned to two groups: the ketanserin group received a loading dose of ketanserin 10 mg i.v. in 2 ml solvent, followed by an i.v. infusion of 0.075 mg $kg^{-1}$ $h^{-1}$; the placebo group received a bolus dose of solvent 2 ml i.v., followed by an i.v. infusion of solvent.

All operations were performed by the same surgeon, with the patients in a lateral position. The acetabular and femoral prostheses were fixed with two-component methylmethacrylate cement. Osteotomy of the greater trochanter was not carried out.

Patients were given diazepam 10 mg orally and atropine 0.5 mg s.c., 1 h before surgery. General anaesthesia was induced with thiopentone 4 mg $kg^{-1}$ and fentanyl 100–200 µg. The trachea was intubated after neuromuscular block had been produced with a small dose of pancuronium, followed by suxamethonium 1 mg $kg^{-1}$. The patient's lungs were ventilated to normocapnia with a non-rebreathing semi-circle system, using nitrous oxide and oxygen 4 and 2.5 litre $min^{-1}$, respectively. Anaesthesia was maintained with fentanyl 3–7 µg $kg^{-1}$ $h^{-1}$ and enflurane up to 0.8 vol % and pancuronium 10–20 µg $kg^{-1}$, given as required.

A cannula was inserted into a radial artery under local anaesthesia. Two central venous catheters were inserted into the right internal jugular vein. One catheter was used for continuous recording of central venous pressure (CVP) and the other for the administration of ketanserin. All patients received Ringer's lactate solution via an additional peripheral venous cannula. Packed red blood cells were given if intraoperative blood loss exceeded 10 % of calculated blood volume. Trial medication was started immediately after the patient was placed in the lateral position, and was discontinued at the time of tracheal extubation, which also marked the end of study. At the end of surgery, residual neuromuscular block was antagonized with neostigmine and atropine if necessary.

### *Measurements*

Intraoperative blood loss was estimated by weighing swabs and drapes and by collection in suction bottles. Preoperative values of systolic, diastolic and mean arterial pressures (SAP, DAP, MAP) and heart rate (HR) were recorded on the day before surgery. Intraoperative values for SAP, DAP, MAP, CVP, HR, end-tidal partial pressure of carbon dioxide and ECG (lead II) were monitored and recorded continuously. Measurements were started after placing the patient in the lateral position ($t = 0$) and repeated at 20-min intervals.

Before and after the administration of the trial medication, an arterial blood sample was taken for measurement of blood-gas tensions, serum electrolyte and haemoglobin concentrations and PCV. Preoperative and postoperative partial thromboplastin time (PTT), activated partial thromboplastin time (APTT), thrombocyte count and bleeding time (method of [14]) were estimated.

### *Statistical analysis*

Data are presented as mean (SEM). Statistical significance was assessed using Wilcoxon's matched-pairs signed rank test for within-group comparisons, and Wilcoxon's two-sample test for between-group comparisons. All statistical tests were performed two-sided and differences were deemed significant if $P < 0.05$.

## RESULTS

The patient groups did not differ significantly in age, sex, height, weight and ASA classification (table I). There was only one male patient in each group, reflecting the preponderance of female patients presenting for THA [15–17].

Mean intraoperative blood loss was 454 (SEM 66) ml in the ketanserin group and 894 (100) ml in the placebo group (fig. 1) ($P = 0.0044$). The duration of surgery was significantly shorter in the ketanserin group (112 (4.6) min than in the placebo group (134 (5.6) min) ($P = 0.0044$), and rate of intraoperative blood loss was also less in the ketanserin than in the placebo group (4.11 (0.58) ml $min^{-1}$ *vs* 6.67 (0.65) ml $min^{-1}$) ($P = 0.030$).

TABLE I. *Patient characteristics (mean (range or SEM))*

| | Placebo ($n = 8$) | Ketanserin ($n = 9$) |
|---|---|---|
| Sex (M/F) | 1/7 | 1/8 |
| Age (yr) | 75.1 (60–88) | 70.2 (60–88) |
| Height (cm) | 161.6 (2.5) | 171.2 (3.2) |
| Weight (kg) | 74.7 (2.6) | 75.4 (4 0) |

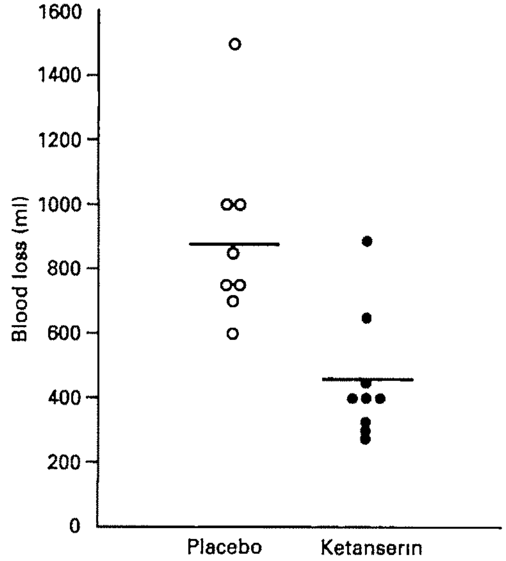

FIG. 1. Intraoperative blood loss for each patient given ketanserin or placebo. Horizontal lines represent mean values (significantly different: $P < 0.01$).

During operation, mean SAP was 108–118 mm Hg in the ketanserin group and 125–140 mm Hg in the placebo group and mean DAP was 59–66 mm Hg and 62–78 mm Hg, respectively, in the two groups. Mean arterial pressure decreased by 10–20% following induction of anaesthesia (fig. 2). During operation, MAP was less in the ketanserin group than in the placebo group, but statistical significance was achieved only at 20 and 60 min after the start of trial medication (fig. 2). Following induction, there was a slight decrease in heart rate, but during operation, heart rate stabilized at 60–75 beat min$^{-1}$ in both groups (fig. 2). Central venous pressures were less in the placebo group than in the ketanserin group, but statistical significance was achieved only at 80 min (fig. 2).

All measurements of coagulation factors, blood-gas tensions and electrolyte concentrations remained within the normal range. Intraoperative loss was replaced promptly with electrolyte solutions and packed cells and there were no differences in PCV and haemoglobin concentration between the two groups. Template bleeding times were similar in both groups at the start and end of the operation (table II). A statistically significant increase in bleeding time was observed in the placebo group, but not in the ketanserin group; however, absolute values stayed within the normal limits (120–570 s). No complications were observed in relation to the use of ketanserin.

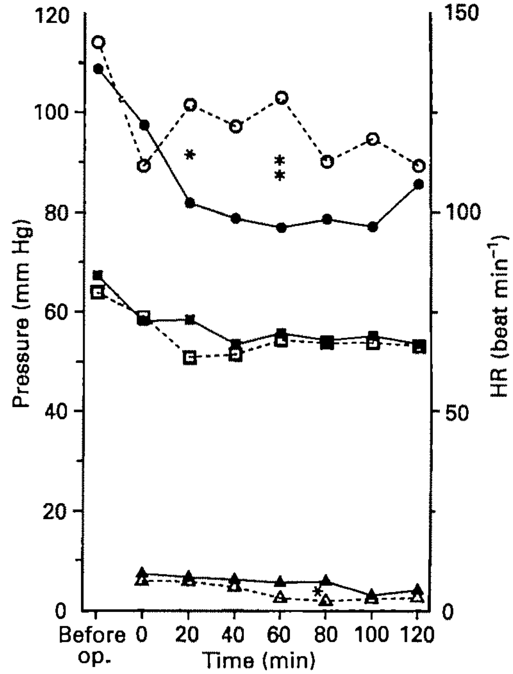

FIG. 2. Haemodynamic changes in patients given ketanserin (solid symbols) or placebo (open symbols). Mean arterial pressure (circles), central venous pressure (triangles), heart rate (HR) (squares). $^*P < 0.05$; $^{**}P < 0.01$ between groups.

TABLE II. *Mean (SEM) template bleeding time at the beginning and end of operation following either placebo or ketanserin.* $^{**}P < 0.01$

| | Bleeding time (s) | | |
|---|---|---|---|
| | Placebo ($n = 8$) | | Ketanserin ($n = 9$) |
| Start | 265 (28) | | 286 (34) |
| End | 371 (30) | | 324 (31) |
| Difference | 116 (26) | ** | 39 (36) |

## DISCUSSION

The present study confirms the hypothesis that ketanserin reduces blood loss during hip arthroplasty under general anaesthesia by virtue of its haemodynamic effects. Ketanserin reduced MAP to a mean intraoperative value of 80 mm Hg, which may be considered safe [4]. Other cardiovascular changes were minor and similar in nature to those accompanying mild induced hypotension. Central venous pressure tended to be greater in the ketanserin group.

As spontaneous ventilation in the lateral position may interfere with alveolar ventilation, all patients' lungs were ventilated mechanically. Theoretically, the resulting increase in intrathoracic pressure would lead to an increase in venous pressure with diminished venous return and subsequent increased bleeding from venous oozing [4,18]. This effect may have been offset by peripheral venodilatation induced by ketanserin. Reduction in peripheral venous pressure reduces venous oozing and is a major factor contributing to diminished blood loss [19]. Thus the reduced blood loss in the ketanserin group may be explained by the combination of a moderate reduction in mean arterial pressure and a reduction in peripheral venous pressure in the surgical wound.

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# EFFECTS OF NITROUS OXIDE ON DAY 9 RAT EMBRYOS GROWN IN CULTURE

## J. M. BADEN AND M. FUJINAGA

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### SUMMARY

*A rat whole embryo culture system was used to study the adverse reproductive effects of nitrous oxide. Embryos were removed on day 9 of gestation and exposed in culture to several concentrations of nitrous oxide for 24 h. After an additional 25 h of culture, embryos were examined for morphological abnormalities and were assayed later for protein content. Nitrous oxide resulted in growth retardation and an increased incidence of morphological abnormalities and altered body laterality. The conditions required to produce abnormalities were similar to those required* in vivo. *We conclude that nitrous oxide has direct toxic effects on the developing embryo and that day 9 embryo culture is a useful technique for studying mechanisms of nitrous oxide-induced teratogenicity.*

***KEY WORDS***
*Anaesthetics, gases: nitrous oxide Toxicity: fetal*

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Fink, Shepard and Blandau first reported in 1967 that nitrous oxide was teratogenic in rats [1]. Since then, many studies have indicated that continuous exposure to 50% or more nitrous oxide for 24 h on either day 8 or 9 of gestation results in increased incidences of fetal wastage, and skeletal and visceral abnormalities in fetuses examined at near full term [2–10]. Recently, we have been developing an *in vitro* rat model to investigate the mechanisms of nitrous oxide teratogenicity which cannot easily be determined using an *in vivo* model. We reported previously studies of day 10 embryos exposed to a single concentration of nitrous oxide [11]. Although useful for establishing the methodology, day 10 embryos are of limited use for studying the teratogenic effects of nitrous oxide [3]. Our primary aim in the present study was to apply the whole embryo culture model to day 9, when embryos are known to be sensitive to the effects of nitrous oxide *in vivo*. Other aims were to establish the types of morphological abnormalities produced by nitrous oxide and their dose–response relationships.

### MATERIALS AND METHODS

Sprague–Dawley rats were obtained from a breeder (Hilltop Lab Animals, Scottdale, Pennsylvania), housed two per cage and provided with food and water on demand. Temperature in the animal room was maintained at 21–24 °C and artificial lighting was provided between 06:00 and 18:00 each day. Pregnancy was achieved by mating the rats for 2 h between 08:00 and 10:00. A copulatory plug was sought immediately after mating, and when found, day 0 of gestation was recorded.

The general methods that we used for removing and culturing embryos were described by New [12]. Briefly, at 08:00 on day 9 of gestation (presomite stage), the rats were killed with carbon dioxide and their uteri excised immediately. Individual implantations consisting of egg cylinders surrounded by decidua were harvested into a sterile Petri dish containing Hank's balanced salt solution. The decidua was dissected from each egg cylinder under a dissecting microscope. Embryos at various stages of culture are shown in figure 1; a day 8 embryo (fig. 1A) has

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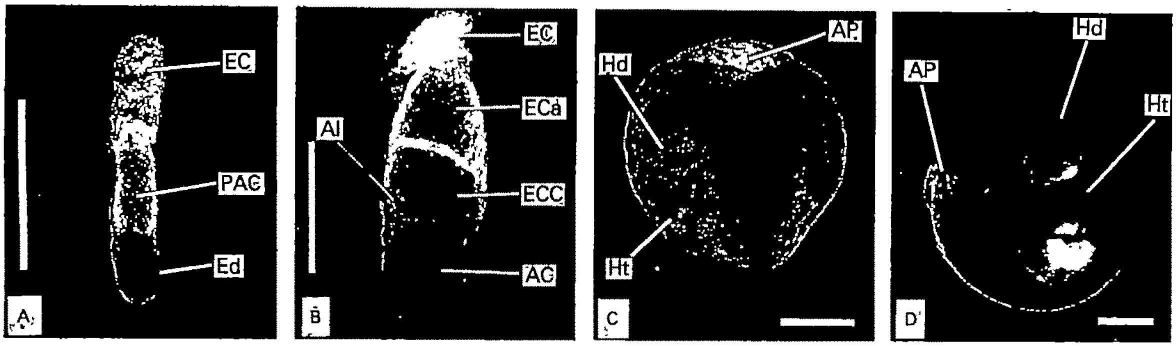

FIG. 1. A: Day 8 embryo (primitive streak stage). B: Day 9 embryo (presomite stage): the egg cylinder has three visible compartments—ectoplacental (epiamniotic) cavity, extraembryonic coelomic cavity and amniotic cavity; the embryo has a rudimentary neural plate but no somites. C: Day 10 embryo, facing to the left and the tail is dorsally flexed. The bulge below the head is the primitive heart. The embryo at this stage has approximately 10 somites. D: Day 11 embryo, now ventrally flexed with the tail on the right side. AC = Amniotic cavity; Al = allantois; AP = allantoic placenta; EC = ectoplacental cone; ECa = ectoplacental cavity; ECC = extraembryonic coelomic cavity; Ed = embryonic disc; Hd = head; Ht = heart; PAC = proamniotic cavity. Bar represents 1 mm.

been included for comparison. Reichert's membrane was removed from the egg cylinder starting from the side opposite to the embryonic disc after the ectoplacental cone and roof of the ectoplacental cavity had been excised [13]. Three to five embryos were placed in a single glass culture bottle (60-ml volume) containing 0.5 ml/embryo of heat-inactivated (56 °C for 30 min), immediately-centrifuged, pregnant rat serum; penicillin 100 u $ml^{-1}$ and streptomycin 50 µg $ml^{-1}$ were added to each bottle to prevent bacterial growth. Bottles were flushed for 2 min with a premixed gas containing 0% (control), 5%, 25% or 75% nitrous oxide in 5% oxygen, 5% carbon dioxide and the balance nitrogen. Bottles were capped with rubber stopcocks and rotated at 20 r.p.m. in a 37–38 °C incubator (09:00). After 24 h, all bottles were flushed with a gas mixture of 5% oxygen, 5% carbon dioxide and 90% nitrogen. Bottles were reflushed with a gas mixture of 20% oxygen, 5% carbon dioxide and 75% nitrogen at 12:00 on day 10 (additional 1.0 ml/embryo of non-pregnant female rat serum was added), and with a gas mixture of 95% oxygen and 5% carbon dioxide at 07:00 on day 11. Oxygen concentrations need to be increased during culture because of the steady increase in oxygen demand of embryos as they age [12]. Oxygen, carbon dioxide and nitrous oxide concentrations were monitored before and after each change of atmosphere using a Datex 254 airway gas monitor (Datex Medical Instrumentation, Inc., Tewksbury, Massachusetts). At 10:00 on gestational day 11, culture was terminated and embryos were examined for crown–rump length, somite number and gross morphology, including sidedness of the allantoic placenta, tail and heart (bulboventricular loop). Embryos were frozen in sodium phosphate buffer 0.1 mol $litre^{-1}$ (pH 7.4) and their protein content measured later [14].

Groups were compared statistically using the chi-square test for discontinuous variables; one-way analysis of variance for continuous variables with Student's *t* test was used as a *post-hoc* test. $P < 0.05$ was considered significant.

## RESULTS

Treatment with nitrous oxide resulted in embryos with smaller crown–rump length, somite number and protein content in the 25% and 75% nitrous oxide groups compared with those in the control group (table I). An increased incidence of altered body laterality and malformations was observed only in the 75% nitrous oxide group (table I). About 30% of embryos had some laterality change, mainly inverted heart (table I). Of 12 embryos with malformations in the 75% nitrous oxide group, five had normal body but small head size (fig. 2B); three of these had pairs of fused somites. The other seven embryos were both small in size and had severe malformations (fig. 2C).

TABLE I. *Morphological and biochemical results from day 11 embryos after culture from day 9 of gestation (number, or mean* (SD)*). *$P < 0.05$ vs control*

| | Control | 5 % $N_2O$ | 25 % $N_2O$ | 75 % $N_2O$ |
|---|---|---|---|---|
| No. of embryos cultured | 90 | 59 | 58 | 58 |
| No. of malformed embryos (excluding laterality changes) | 0 | 1 | 1 | 12* |
| No. of normal embryos | 90 | 58 | 57 | 46 |
| No. of embryos with laterality changes | | | | |
| Left sided tail | 2 | 0 | 2 | 9* |
| Left side allantoic placenta | 0 | 0 | 3* | 8* |
| Inverted heart | 3 | 1 | 6 | 15* |
| Any laterality change | 5 | 1 | 7 | 18* |
| Crown–rump length (mm) | 3.2 (0.3) | 3.2 (0.2) | 3.0 (0.2)* | 3.0 (0.3)* |
| Somite number | 24.4 (1.7) | 23.9 (1.3) | 23.1 (1.2)* | 23.7 (1.7)* |
| Protein content (µg/embryo) | 120 (20) | 125 (22) | 111 (19)* | 111 (24)* |

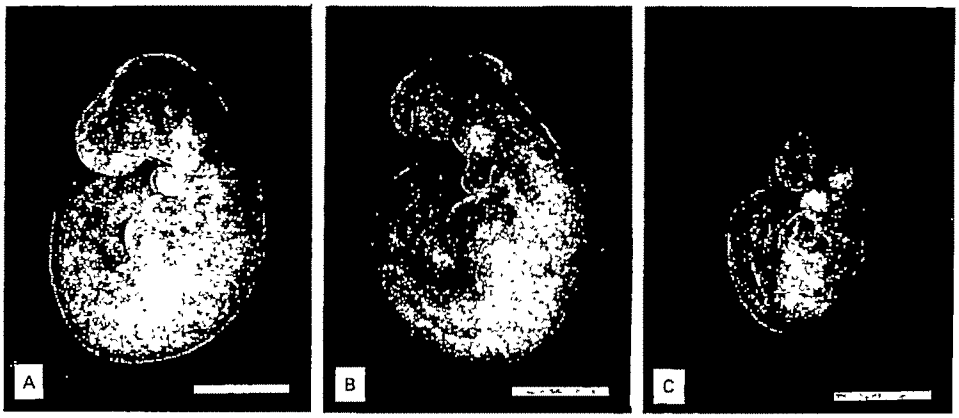

FIG. 2. A: Normal day 11 embryo. B: Day 11 embryo treated with 75 % nitrous oxide for 24 h from day 9. The embryo has a relatively small head compared with other parts of the body. C: Day 11 embryo treated with 75 % nitrous oxide. The embryo is smaller than normal and is severely malformed. Bar represents 1 mm.

## DISCUSSION

In the present study, we have demonstrated that rat embryos grown in culture are susceptible to adverse effects of nitrous oxide administered on day 9 of gestation. Effects were more frequent and more severe than those observed previously after day 10 exposure [11]. This pattern of sensitivity is similar to that seen *in vivo* [3].

The concentrations of nitrous oxide required to produce significant effects were also similar to those required *in vivo* [3, 7, 8]. In particular, the morphological abnormalities and altered body laterality occurred only at the 75 % concentration, as they would after *in vivo* exposure. In contrast, mild growth retardation identified by decreased somite number, crown–rump length and protein content occurred even at a concentration of 25 %, which produces neither teratogenesis nor growth retardation *in vivo* [7, 8]. Presumably growth catches up by gestational day 20 when fetuses are examined after *in vivo* exposure.

It is important to understand the general limitations of whole embryo culture when interpreting our data. First, only a portion of the period of gestation (routinely, days 9–11) can be studied satisfactorily. For some teratogens, this may not be the period in which abnormalities are produced. For nitrous oxide, however, embryos are especially sensitive on day 9. Another consequence of this limited experimental period is that the fate of embryos with morphological and biochemical changes observed after culture may be uncertain. In the present study, embryos with minor morphological abnormalities would probably survive and their teratogenic effects be revealed. For example, those observed on day 11 with fused somites would be observed as having rib or vertebral abnormalities at full term. Many of those with major morphological abnormalities, however, would not survive and would be seen as resorptions at full term. Most embryos with altered body laterality (left-sided tail and inverted bulboventricular loop) were normal in size and general morphology and would probably survive until full term when their *situs inversus* would be revealed. A second limitation for many teratogens is that it may be necessary for them to be metabolized in the mother before they become teratogenic. This is not the case with nitrous oxide because it is not metabolized by mammalian tissues. Furthermore, its only known biochemical reaction, oxidation of vitamin $B_{12}$, is non-enzymatic and is independent of the immature enzyme system of the embryo. Finally, pharmacokinetic differences between exposure of embryos *in utero* and in culture may be considerable for many teratogens. Again, this is unlikely to be important for nitrous oxide because it is a highly lipid soluble compound that equilibrates rapidly throughout all tissues.

Although our day 9, *in vitro* model has limitations, it also has some advantages over the *in vivo* model. First, it enabled us to identify many direct effects of nitrous oxide on developing embryos. This does not preclude the possibility that maternally-mediated effects occur also, but probably limits them to a minor role. Indeed, we have speculated previously that decreased uterine blood flow caused by sympathomimetic action accounts for some of the adverse reproductive effects caused by nitrous oxide [15]. Our finding that phenoxybenzamine did not prevent the morphological abnormalities produced by nitrous oxide, although it should have prevented the decreased uterine blood flow, is consistent with the minor role played by maternally-mediated effects [15]. A second advantage of the *in vivo* model is that it may enable investigators to control experimental conditions closely during embryonic development in a manner not possible *in vivo*. This advantage is critical for future studies on the mechanisms of nitrous oxide-induced teratogenicity, such as the relative contribution of adrenergic stimulation and methionine synthase inhibition. These studies should provide insight into such fundamental developmental processes as body laterality.

## ACKNOWLEDGEMENTS

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# MYOCARDIAL METABOLISM DURING ANAESTHESIA WITH PROPOFOL—LOW DOSE FENTANYL FOR CORONARY ARTERY BYPASS SURGERY

K. M. VERMEYEN, S. G. DE HERT, F. A. ERPELS
AND H. F. ADRIAENSEN

## SUMMARY

*We have studied the haemodynamic and myocardial effects of propofol–fentanyl anaesthesia in 12 patients undergoing coronary artery bypass surgery during the pre-bypass period. The induction dose of propofol was 1.5 mg kg$^{-1}$ and mean infusion rate during maintenance was 4.48 mg kg$^{-1}$ h$^{-1}$ (range 1.87–7.24 mg kg$^{-1}$ h$^{-1}$). The total dose of fentanyl was 30 μg kg$^{-1}$. The haemodynamic changes indicated myocardial depression and peripheral vasodilatation. Coronary sinus flow and indicators of global myocardial perfusion (myocardial oxygen consumption, myocardial lactate extraction) did not change. Although not excluding regional myocardial ischaemia, these results show that propofol–fentanyl anaesthesia has no major adverse effects on cardiac function.*

**KEY WORDS**
*Anaesthesia. cardiovascular. Anaesthetics Intravenous · propofol. Heart: blood flow, myocardial.*

Cardiac work and myocardial oxygen consumption should not be allowed to increase during anaesthesia for coronary artery bypass grafting (CABG). Controlled reduction in cardiac work and myocardial oxygen demand is thought to be beneficial in these patients [1]. The myocardial depression caused by propofol and its effect on the circulation might be useful for this purpose [2, 3]. However, propofol may cause significant reduction in systemic arterial pressure following induction of anaesthesia [3] and during continuous infusion [4], and impairment of myocardial oxygenation has been described [5, 6]. We have studied, therefore, the effects of propofol combined with low dose fentanyl in patients with good myocardial function undergoing CABG.

## PATIENTS AND METHODS

With the approval of the Ethics Committee of the University Hospital Antwerp, we studied 12 male adult patients with good left ventricular function (ejection fraction > 0.45; left ventricular end-diastolic pressure < 13 mm Hg) during CABG. All patients had angiographically proven coronary artery disease. No patient had significant left main coronary artery stenosis. All gave full informed consent to the study.

Patient characteristics are summarized in table I. All patients were taking beta-adrenoreceptor blocking or calcium-channel blocking drugs, or both, and continued their normal oral medication until the morning of surgery.

Premedication was given 1 h before the start of the procedure and comprised i.m. fentanyl 2 μg kg$^{-1}$, droperidol 0.01 mg kg$^{-1}$ and glycopyrrolate 0.03 mg kg$^{-1}$.

In the operating room, the electrocardiogram (lead I, II and V5) was monitored continuously. Two large-gauge venous cannulae and a 20-gauge arterial cannula were inserted. A 7-French gauge flow-directed balloon-tipped thermodilution catheter was introduced into the pulmonary artery via the right internal jugular vein. A Baim coronary sinus (CS) thermodilution catheter (Elecath Corp., Rahway, NJ) [7, 8] was placed via a second introducer in the right internal jugular vein. Mid CS position of the Baim catheter was checked using fluoroscopy and injection of contrast medium. Using this type of catheter, it is possible to assess rapid changes in coronary blood

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TABLE I. *Patient characteristics. BSA = body surface area; NYHA Class = New York Heart Association classification; Grafts = number of venous grafts + int. mammary artery graft; AMI = acute myocardial infarction; HT = hypertension. Medication: A = atenolol; N = nifedipine; I = isosorbide; P = propranolol; S = sotalol*

| Patient No. | Age (yr) | Weight (kg) | BSA ($m^2$) | NYHA class (I–IV) | Grafts | AMI | HT | Medication |
|---|---|---|---|---|---|---|---|---|
| 1 | 53 | 70 | 1.79 | IV | 4+1 | – | + | A/N/I |
| 2 | 60 | 77 | 1.98 | III | 2+1 | – | – | A/I |
| 3 | 38 | 89 | 2.12 | III | 4+1 | – | – | N/I |
| 4 | 52 | 92 | 2.20 | III | 4+1 | + | – | N/I |
| 5 | 58 | 75 | 1.86 | III | 3+1 | – | – | A/I |
| 6 | 57 | 80 | 1.94 | II | 0+1 | – | – | P/T/I |
| 7 | 50 | 76 | 2.15 | III | 4+1 | – | + | S/N/I |
| 8 | 53 | 76 | 1.93 | III | 3+1 | + | – | A/I |
| 9 | 59 | 85 | 2.09 | III | 4+1 | – | + | A/N/I |
| 10 | 65 | 73 | 1.90 | III | 4+1 | – | – | A/I |
| 11 | 54 | 91 | 2.17 | III | 4+1 | + | – | N/I |
| 12 | 43 | 94 | 2.22 | IV | 4+1 | + | + | A/N |

flow and to sample CS blood. The indicator for CS blood flow measurement was normal saline at room temperature injected at 50 ml $min^{-1}$ via a syringe pump. All cannulae were inserted under local anaesthesia and pressure measurements were checked for adequate dynamic response [9].

Standard haemodynamic measurements were obtained and cardiac index (CI), systemic vascular resistance (SVR) and left ventricular stroke work index (LVSWI) were calculated using standard formulae. In calculating coronary vascular resistance and derived variables for myocardial oxygenation, we assumed that CS blood was representative of total coronary blood flow.

Arterial, mixed venous and CS blood samples were obtained for measurement of lactate and haemoglobin concentrations and oxygen saturation. Lactate was measured using the LDH–NAD enzymatic method (ACA-DuPont Company), which has a sensitivity of 0.1 mmol $litre^{-1}$ [10]. Data were recorded and calculated at the following times: at the end of a 10-min stabilization period after insertion of the catheters (T1), 3 min after induction of anaesthesia (T2), 3 min after tracheal intubation (T3), just before and 3 min after sternotomy (T4 and T5) and just before aortic cannulation (T6) when the CS catheter was removed.

During the observation period the presence of myocardial ischaemia was assumed if there was ST-depression of 0.1 mV in $V_5$ or 0.2 mV in the peripheral leads, or both, and increased pulmonary capillary wedge pressure (PCWP) or the appearance of prominent v-waves on the PCWP tracing.

Anaesthesia was induced with diazepam 0.1 mg $kg^{-1}$, fentanyl 8 μg $kg^{-1}$, pancuronium 0.1 mg $kg^{-1}$ and propofol 1.5 mg $kg^{-1}$ given in sequence and maintained with a continuous propofol infusion at a maximum rate of 9 mg $kg^{-1}$ $h^{-1}$. The infusion rate was adjusted in response to changes in SAP. In order to provide sufficient analgesia, increments of fentanyl (to a total dose of 22 μg $kg^{-1}$) were given at sternotomy.

The lungs were ventilated with 100% oxygen and the ventilator frequency and tidal volume were adjusted to maintain $Pa_{CO_2}$ at 4.7–5.3 kPa. All patients received crystalloid fluid 10 ml $kg^{-1}$ i.v. in the pre-bypass period in order to maintain PCWP at preinduction values. Myocardial protection was obtained with intermittent aortic cross clamping and lidoflazine 1 mg $kg^{-1}$ i.v. before the start of cardiopulmonary bypass. After surgery, serial cardiac enzymes (CKtot, CK-MB, ALAT, ASAT) and ECG morphology were analysed.

Results were analysed for statistical significance, using analysis of variance for repeated measurements (ANOVA). Where appropriate, this was followed by the Scheffé *F* test. Statistical significance was accepted at $P < 0.05$.

## RESULTS

Haemodynamic and myocardial data are summarized in tables II and III for systemic and coronary circulations, respectively. The mean duration of the study was 80 min (range 59–124 min). The mean infusion rate of propofol was 4.48 (SD 0.58) mg $kg^{-1}$ $h^{-1}$ (range 1.87–7.24).

Induction of anaesthesia was associated with

TABLE II. *Haemodynamic data (mean (SEM)). T1 = Ten minutes after insertion of the catheters; T2 = 3 min after induction; T3 = 3 min after intubation; T4 = just before sternotomy; T5 = 3 min after sternotomy; T6 = just before aortic cannulation. HR = heart rate; SAP = systolic arterial pressure; DAP = diastolic arterial pressure; PCWP = pulmonary capillary wedge pressure; CI = cardiac index; SVR = systemic vascular resistance; LVSWI = left ventricular stroke work index; TB$\dot{V}o_2$ = total body oxygen consumption.* * *Significant difference compared with T1* ($P < 0.05$)

| | T1 | T2 | T3 | T4 | T5 | T6 |
|---|---|---|---|---|---|---|
| HR (beat $min^{-1}$) | 63 (3) | 69 (3) | 66 (3) | 60 (3) | 62 (3) | 64 (2) |
| SAP (mm Hg) | 126 (4) | 91 (3)* | 107 (5)* | 117 (3) | 119 (5) | 109 (5) |
| DAP (mm Hg) | 61 (2) | 45 (2)* | 55 (2) | 62 (2) | 65 (3) | 60 (3) |
| CI (litre $min^{-1}$ $m^{-2}$) | 3.05 (0.17) | 3.11 (0.15) | 2.93 (0.11) | 2.57 (0.10)* | 2.62 (0.08) | 2.54 (0.13)* |
| PCWP (mm Hg) | 13 (1) | 14 (1) | 13 (1) | 13 (1) | 12 (1) | 12 (1) |
| SVR (dyn s $cm^{-5}$) | 1010 (66) | 706 (54)* | 893 (51) | 1140 (64) | 1151 (75) | 1116 (92) |
| LVSWI (g m $m^{-2}$) | 55 (3) | 38 (3)* | 44 (3)* | 47 (2) | 48 (2) | 42 (3)* |
| TB$\dot{V}o_2$ (ml $min^{-1}$) | 261 (16) | 230 (25)* | 188 (15)* | 184 (20)* | 179 (19)* | 172 (15)* |

TABLE III. *Myocardial variables (mean (SEM)). Measurement times as in table II. CSF = Coronary sinus flow; CVR = coronary vascular resistance; M$\dot{V}o_2$ = myocardial oxygen consumption; MLE = myocardial lactate extraction; $MO_2E$ = myocardial oxygen extraction; $MO_2A$ = myocardial oxygen availability*

| | T1 | T2 | T3 | T4 | T5 | T6 |
|---|---|---|---|---|---|---|
| CSF (ml $min^{-1}$) | 122 (7) | 116 (10) | 121 (8) | 100 (8) | 100 (8) | 101 (9) |
| CVR (mm Hg $min^{-1}$ ml) | 0.42 (0.02) | 0.31 (0.03) | 0.38 (0.04) | 0.52 (0.04) | 0.55 (0.05) | 0.52 (0.07) |
| M$\dot{V}o_2$ (ml $min^{-1}$) | 11.65 (1.10) | 10.77 (0.95) | 11.84 (1.00) | 10.56 (0.69) | 10.55 (0.92) | 10.19 (1.25) |
| MLE (%) | 36.3 (4.5) | 41.7 (3.1) | 39.3 (3.6) | 40.1 (5.3) | 39.3 (3.5) | 35.4 (4.4) |
| $MO_2E$ (%) | 58.1 (3.4) | 52.4 (0 1) | 55.2 (2.8) | 62.7 (2.1) | 63.8 (1.9) | 60.3 (3.6) |
| $MO_2A$ (ml $min^{-1}$) | 19.9 (1.4) | 21.0 (1.9) | 21.8 (1.4) | 17.6 (1.5) | 17.3 (1.7) | 17.4 (1.9) |

significant decreases in SAP (28%) and DAP (26%) (range 72–101 mm Hg and 32–54 mm Hg, respectively). CI was sustained in the presence of a reduced SVR (30%) while LVSWI decreased by 31% and this persisted through the study. Before sternotomy, arterial pressure had returned to preinduction values. At this time, CI was reduced, with a slightly greater SVR. Three patients had an SAP greater than their preinduction value after sternotomy, but in none did it exceed 137 mm Hg. Tachycardia was not observed, the fastest rate being 90 beat $min^{-1}$ at T2. Total body oxygen consumption decreased by 12% after induction and remained significantly reduced during maintenance. Coronary sinus flow, mean coronary vascular resistance, myocardial oxygen consumption and myocardial lactate extraction were unchanged throughout. Myocardial ischaemia (peaked v-wave on the PCWP recording) occurred in only one patient at T5. Global myocardial oxygenation was within normal limits. All patients were weaned readily from CPB and cardiac enzymes (CK, CK-MB, LDH, ASAT, ALAT) were within normal limits after completion of surgery. Postoperative ECG recordings showed no evidence of additional heart muscle damage, compared with preoperative ECG recordings.

## DISCUSSION

The haemodynamic changes observed in this study are similar to those of previous reports with propofol, both for induction and for maintenance [2–4, 11]. The myocardial depressant [12] and vasoactive [11] effects of propofol were associated with cardiovascular stability during tracheal intubation, sternotomy and sternal spread, without the need for vasodilator therapy. This haemodynamic stability is in contrast with studies using high dose opioids [13–15] where the incidence of hypertension was high.

The transient but important changes after induction could probably have been reduced by using a smaller induction dose of propofol. As flow through a significant isolated stenosis may be pressure dependent, patients with left main coronary artery stenosis were excluded from this study for ethical reasons. Therefore it is difficult to extrapolate our results to this patient population. The significant decrease in diastolic arterial pressure on induction of anaesthesia might reduce global coronary perfusion. However, we found no reduction in coronary perfusion, presumably because of coronary autoregulation. Myocardial oxygen consumption remained at basal values throughout the study and there was no evidence of anaerobic metabolism as assessed by myocardial lactate extraction (MLE). According to Ihlen and colleagues [16], an MLE of 15% or less is indicative of ischaemia. One patient in the present study had an MLE of 18% at T6. This patient had a peaked v-wave on the PCWP recording, but normal ECG tracing at T5 when MLE was 30%. Sampling of CS blood and measuring CSF only permits global evaluation of myocardial metabolism [17], and regional ischaemia can not be excluded.

The effects of propofol on myocardial blood flow and metabolism in coronary artery surgery have been studied also by Stephan and colleagues [5]. They found a reduction in myocardial blood flow and oxygen consumption, and an increase in coronary vascular resistance. In two patients they observed lactate production: in one following induction of anaesthesia with propofol 2 mg $kg^{-1}$ and in one following sternotomy when the dose of propofol was 12 mg $kg^{-1}$ $h^{-1}$ and that of fentanyl 10 µg $kg^{-1}$. It is difficult to compare these results with ours. First, an inert gas method (argon) was used to measure myocardial blood flow, which is not directly comparable to CS blood flow. Second, the dose of propofol was more than twice that used in the present study and the dose of fentanyl much less. Finally, their awake measurements showed a mean MLE of 13.9 (9.4) %, which may indicate borderline myocardial ischaemia [16, 18].

Moffit [1] concluded that it is difficult to maintain a normal myocardial oxygen supply–demand balance using a single anaesthetic agent. The combination of a moderate dose of opioids with an inhalation agent is considered to be more efficient in controlling haemodynamic variables and maintaining myocardial oxygenation. Inhalation agents are used to decrease cardiac work and thus decrease myocardial oxygen consumption. Using the myocardial depressant effects of propofol, we were also able to control left ventricular work and myocardial oxygen consumption. In contrast, studies using single anaesthetic techniques with isoflurane [19], halothane [19] or propofol [5] reported a significant incidence of myocardial ischaemia.

We conclude that propofol in combination with a moderate dose of fentanyl is a suitable anaesthetic technique for CABG.

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# PACEMAKER FAILURE ON INDUCTION OF ANAESTHESIA

S. R. FINFER

## *SUMMARY*

*A patient with a permanent pacemaker presented for repair of a strangulated hernia. During induction of anaesthesia, the pacemaker generator stopped discharging, thus causing cardiac arrest. The likely cause of the generator failure was inhibition by suxamethonium-induced muscle fasciculations. Following defibrillation, an increase in stimulation threshold necessitated urgent insertion of a transvenous pacing system. It is suggested that, when suxamethonium is to be used in a patient with a permanent pacemaker, consideration should be given to reprogramming the pacemaker to asynchronous mode before induction of anaesthesia. If a patient with a pacemaker requires defibrillation, an acute increase in stimulation threshold may result and cause loss of capture. Rapid insertion of a transvenous pacing system may be necessary.*

***KEY WORDS***
*Anaesthesia, general. Complications: pacemaker failure Neuromuscular relaxants: suxamethonium.*

## CASE REPORT

An 81-yr-old lady was diagnosed as having a strangulated hernia with intestinal obstruction, and was scheduled for emergency surgery. She had a Medtronics Activitrax 8403 (Medtronic Inc., Minneapolis, U.S.A.) permanent pacemaker *in situ*.

She denied symptoms of ischaemic heart disease or congestive cardiac failure, but was known to have functional tricuspid incompetence. She was receiving frusemide 80 mg, warfarin 4 mg and thyroxine 0.1 mg per day.

On examination, her weight was estimated at 50 kg, she appeared euthyroid, arterial pressure was 170/90 mm Hg, heart rate 70 beat $\text{min}^{-1}$ and regular. The chest was clear to auscultation. On admission, full blood count and serum concentrations of urea, sodium and potassium were within the normal range and the prothrombin ratio (INR) was 2.4.

Chest radiograph showed the presence of a pacemaker generator in the upper left chest wall; the lead appeared intact and the tip was positioned at the apex of the right ventricle. The admission ECG showed the pacemaker was functioning and was inhibited appropriately by intrinsic ventricular beats (fig. 1).

Despite the fact that she was clearly a high risk patient, it was decided to proceed to surgery without delay. Premedication was not prescribed.

On arrival of the patient in the operating theatre, continuous ECG and non-invasive automatic arterial pressure monitoring were commenced. The ECG monitor showed the pacemaker was functioning and the arterial pressure was stable. After 5 min preoxygenation, anaesthesia was induced with thiopentone 125 mg and fentanyl 0.05 mg, cricoid pressure was applied and neuromuscular block produced with suxamethonium 50 mg. During tracheal intubation, the audible QRS bleep from the ECG monitor ceased and the monitor showed asystole with no visible pacemaker artefact; the carotid pulse was sought, but was not palpable. External cardiac massage was commenced and the lungs were ventilated with 100% oxygen. On rechecking the ECG monitor, ventricular fibrillation was seen. A 50-J direct current shock was administered; this resulted in an idioventricular rhythm with a rate of approximately 35 beat $\text{min}^{-1}$, and a systolic arterial pressure of 90 mm Hg. A second episode of ventricular fibrillation responded also to defibrillation, following which slow idioventricular rhythm was maintained. The patient was sedated

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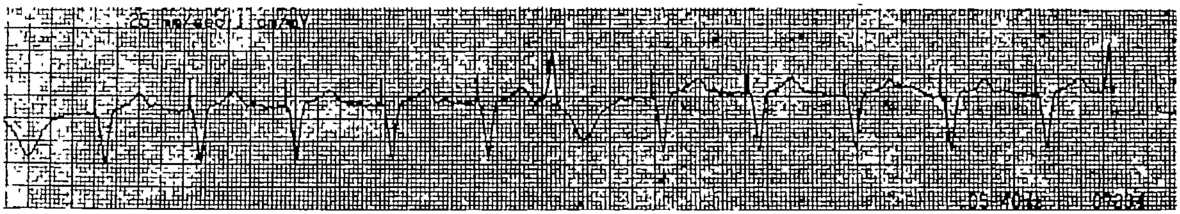

FIG. 1. ECG on admission. Shows pacemaker artefacts with reliable capture, and inhibition by a spontaneous ventricular discharge.

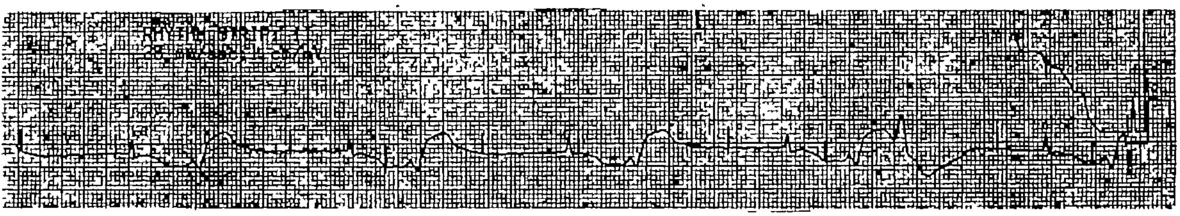

FIG. 2. ECG on arrival in the Intensive Care Unit. Shows idioventricular rhythm and pacemaker artefacts with complete failure of both capture and inhibition.

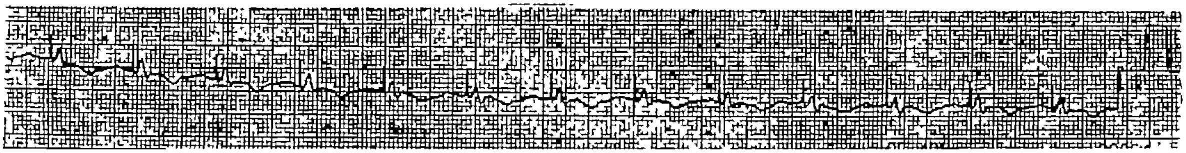

FIG. 3. ECG after insertion of the temporary pacemaker with reliable capture re-established.

with midazolam and neuromuscular block was maintained with pancuronium. An i.v. infusion of isoprenaline was begun and a ventricular rate of approximately 70 beat $\text{min}^{-1}$ maintained. She was transferred to the Intensive Care Unit. The permanent pacemaker continued to discharge, as indicated by the presence of pacing artefacts on the ECG, but there was complete failure of both capture and inhibition (fig. 2).

Serum concentrations of sodium and potassium were measured and again found to be within the normal range. A temporary transvenous pacing wire was inserted and connected to an external pacing source. This system re-established reliable cardiac pacing (fig. 3).

Following a period of stabilization, the patient was returned to the operating theatre; the mass in her groin was explored and found to be a rectus sheath haematoma. After operation, she was returned to the Intensive Care Unit. She made a good recovery and had no neurological deficit. Serial measurement of serum concentrations of cardiac enzymes for the next 3 days were within the normal range. Biochemical tests of thyroid function were also within normal limits. The temporary pacing system continued to function and she was transferred to the regional cardiology centre, where the function of the permanent pacemaker was checked. The generator was found to be functioning normally with an output of 2.7 V and a pulse width of 0.5 ms, but the stimulation threshold was greater than 4 V at a pulse width of 0.5 ms. A new permanent pacing lead was inserted and connected to the generator, and this resulted in a functioning system. The stimulation threshold of the new lead was 0.38 V at 0.5 ms. When the patient had recovered adequately from her surgery, she was discharged home.

## DISCUSSION

In this patient, the pacemaker generator discharge ceased during induction of anaesthesia and intubation of the patient's trachea. The likely cause of this failure was inhibition of the generator by myopotentials. It has been suggested that the muscle fasciculations produced by suxamethonium might cause myopotential-mediated inhibition of pacemaker function [1]; however the author is not aware of any previous report of this occurring in clinical practice.

It is well known that unipolar pacemaker systems may be inhibited by skeletal muscle myopotentials. This phenomenon was described first in 1972 [2] and may occur in 11–85% of patients with pacemakers [3–5]. It occurs with both single and dual chamber pacemakers [6]. The majority of patients are asymptomatic and inhibition may be detected only by exercise testing or by long term Holter monitoring of the ECG. Inhibition may lead to long asystolic pauses [4] which may be followed by serious ventricular arrhythmias [7].

This patient's generator was a Medtronic Activitrax 8403 model. This is a multiprogrammable, single chamber demand pacemaker with automatic rate variability. It is designed to increase the rate of the generator discharge in response to exercise. The activity sensing system consists of a piezo-electric sensor bonded to the inside of the generator casing. The muscle fasciculation caused by suxamethonium may have caused stimulation of the piezo-electric sensor. However, there is no known mechanism by which excess stimulation of the sensor causes inhibition of the pulse generator.

Following resuscitation, the pacemaker generator was functioning normally, but with failure of both capture and inhibition. When the system was checked, the stimulation threshold was found to be greater than 4 V at a pulse width of 0.5 ms; the generator settings were unchanged (pulse amplitude 2.7 V, pulse width 0.5 ms). Therefore, the failure of capture and inhibition was caused by an acute increase in stimulation threshold. The patient was defibrillated twice during resuscitation. Modern pacemakers incorporate protective circuits to shield the complex electronics of the generator from the energy delivered to the body during defibrillation. These circuits result in shunting of energy away from the internal electronics of the generator to the electrode. Thus defibrillation may result in endocardial burns and fibrosis at the electrode–endocardium interface and this may result in an increase in stimulation threshold [8].

Suxamethonium is the neuromuscular blocking agent of choice for patients requiring a rapid sequence induction of anaesthesia. Where suxamethonium is to be used in a patient with a unipolar demand pacemaker, it would seem advisable to switch the pacemaker to asynchronous mode before the drug is administered. This is achieved most readily by use of a precordial magnet. However, this increases the risk of arrhythmias secondary to the "R on T" phenomenon, and may allow unintentional reprogramming of certain pacemakers [9]. As a result, some authors have suggested that the routine use of a precordial magnet is potentially dangerous [10]. It should be remembered that the precise effect of placing a magnet over the generator depends on the type of generator and on its programmed settings. These should be ascertained before application of the magnet, or serious complications may result [11].

If a magnet is used during administration of suxamethonium it may be removed when muscle fasciculations have subsided.

If defibrillation is required in a patient with a pacemaker, the paddles should be positioned as far away from the pacemaker generator as possible. If possible, anterior to posterior positioning of the paddles should be used. The minimum energy necessary for defibrillation should be used. However, even with these precautions, defibrillation may result in an acute increase in the stimulation threshold, with resultant loss of capture. If this occurs, either immediate reprogramming of the pacemaker to increase generator output or rapid insertion of a temporary pacing system may be necessary.

Despite the number of patients with pacemakers that have undergone anaesthesia and surgery uneventfully, and the increased safety of modern pacemaker systems, anaesthetists should be prepared for the occurrence of unexpected pacemaker-related problems in patients under their care.

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# HELLP SYNDROME: A CASE REPORT WITH GUIDELINES FOR DIAGNOSIS AND MANAGEMENT

## K. W. PATTERSON AND D. P. O'TOOLE

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### SUMMARY

*A 25-yr-old patient with a twin pregnancy of 34 weeks gestation developed HELLP syndrome and required urgent delivery by Caesarean section. Before operation, a central venous catheter and urinary catheter were inserted, and fresh frozen plasma and platelets were administered to correct hypovolaemia and severe thrombocytopenia. This case demonstrates the critical condition of these patients before operation and that extensive preoperative preparation and invasive monitoring are necessary for successful management. The choice of anaesthetic is governed by the presence of liver and renal dysfunction and severe thrombocytopenia.*

***KEY WORDS***
*Anaesthesia: obstetric Complications: HELLP syndrome, pregnancy-induced hypertension, pre-eclamptic toxaemia*

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"Haemolysis (H), elevated liver enzyme activity (EL) and low platelet count (LP)", (HELLP syndrome), named by Louis Weinstein of the University of Arizona, is a rare manifestation of hypertensive diseases of pregnancy and represents the most severe end of the pre-eclampsia spectrum [1]. The syndrome is of interest to the anaesthetist as many of these patients may require urgent delivery by Caesarean section in an effort to halt the disease process. Pregnancies complicated by this syndrome are associated with poor maternal and fetal outcome. The mothers are at high risk of developing acute renal failure, shock lung, abruptio placenta and, occasionally, liver rupture with a maternal mortality in the range 2–24% [2]. This poses a considerable challenge to the anaesthetist, who may be presented at short notice with one of these patients for emergency Caesarean section.

### CASE REPORT

A 25-yr-old woman with a twin pregnancy of 34 weeks gestation was admitted to the maternity unit complaining of nausea and vomiting, epigastric pain and loose bowel motions. She was not in labour on admission and her vital signs were normal. Arterial pressure was 130/80 mm Hg, there was no evidence of peripheral oedema, and urinalysis was negative for protein, glucose and acetone. Her haemoglobin was 11 g% and platelets were 100000 $mm^{-3}$. Her antenatal history was uneventful before this admission.

Over the next 48 h the patient's arterial pressure increased to 160/95 mm Hg and she developed proteinuria and peripheral oedema. Laboratory investigations included haemoglobin (10.4 g%) and a platelet count (22000 $mm^{-3}$). Prothrombin time, activated partial thromboplastin time and serum concentration of fibrinogen were normal; fibrin degradation products were 80 μg $litre^{-1}$ (normal value < 10 μg $litre^{-1}$). Liver function tests included decreased concentrations of total protein (57 g $litre^{-1}$; normal range 60–80 g $litre^{-1}$); albumin 33 g $litre^{-1}$ (normal range 34–48 g $litre^{-1}$); phosphate 0.73 mmol $litre^{-1}$ (normal range 0.8–1.45 mmol $litre^{-1}$); lactic dehydrogenase 295 u $litre^{-1}$ (normal range 60–200 u $litre^{-1}$); alanine aminotransferase 159 u $litre^{-1}$ (normal range 0–45 u $litre^{-1}$); aspartate aminotransferase 200 u $litre^{-1}$ (normal range 0–40 u $litre^{-1}$); bilirubin 18 μmol $litre^{-1}$ (normal range 0–18 μmol $litre^{-1}$). Alkaline phosphatase was normal. A peripheral blood smear showed evidence of a microangiopathic haemolytic anaemia.

At this stage a diagnosis of HELLP syndrome was considered. In view of the rapid progression

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of the disease process and the gestational age of the pregnancy, it was decided to proceed to Caesarean section. The anaesthetic team were informed. A central venous catheter was inserted via the right internal jugular approach and a urinary catheter was inserted to assess intravascular volume and monitor urinary output. Central venous pressure and urinary output were low; 3 mm Hg and 10 ml $h^{-1}$, respectively. Fresh frozen plasma 400 ml was given to increase plasma volume and urinary output. Urinary output increased to 30 ml in the next 1 h. A platelet transfusion (6 units) was also given immediately before surgery to increase the platelet count to more than 50000 $mm^{-3}$. Before the patient was transferred to theatre, an infusion of hydralazine was commenced, as is the practice in this unit, to reduce mean arterial pressure and thus avoid the risk of eclampsia or intracranial haemorrhage.

On arrival of the patient in the operating theatre, her mean arterial pressure was between 100 and 105 mm Hg. Anaesthesia was induced with thiopentone 5 mg $kg^{-1}$ and intubation was facilitated by administration of suxamethonium 1.5 mg $kg^{-1}$ i.v. Fentanyl 5 µg $kg^{-1}$ was given i.v. at induction to attenuate the hypertensive response to intubation. Atracurium 0.6 mg $kg^{-1}$ was used to provide neuromuscular block, and the patient's lungs were ventilated with 50% nitrous oxide and 0.5% isoflurane in oxygen. Two healthy male infants were delivered, weighing 1730 g and 1570 g. The patient's recovery was uneventful. One unit of fresh whole blood was administered during operation, followed by two further units on the first night after operation. The patient was monitored on a high dependency unit within the obstetric department for the first 24 h after operation. Monitoring included: central venous pressure, urinary output, non-invasive arterial pressure, ECG and oxygen saturation.

The infusion of hydralazine was reduced and stopped when arterial pressure was stable after 6 h. On the second day after operation platelet count was 112000 $mm^{-3}$. Liver enzyme concentrations returned to normal over the following week.

## DISCUSSION

Pre-eclampsia is a condition with a spectrum of pathophysiological changes. At the most severe end of this spectrum a syndrome exists comprising haemolysis, increased concentrations of liver enzymes and decreased platelet count (HELLP syndrome). The clinical signs and symptoms of the syndrome include epigastric pain, upper abdominal tenderness, proteinuria, hypertension, jaundice and nausea and vomiting. Progression of the syndrome may lead to haematuria, oliguria, acute tubular necrosis, cortical necrosis and panhypopituitarism. Rarer complications include acute liver rupture and adult respiratory distress syndrome. A non-obstetric diagnosis such as acute cholecystitis, drug reaction or idiopathic thrombocytopenia is often considered at presentation [2–4]. The diagnosis is suspected on clinical grounds and confirmed by laboratory investigations. Severe pre-eclampsia is diagnosed if arterial pressure exceeds 160/90 mm Hg or there is proteinuria $> 5$ g/24 h, oliguria $< 400$ ml/24 h, cerebral signs or pulmonary oedema [5]. If, in addition, there is evidence of haemolytic anaemia, thrombocytopenia and increased liver enzyme activity, HELLP syndrome should be considered [5]. The degree of thrombocytopenia correlates well with the degree of liver dysfunction [6]. Maternal mortality is high—Weinstein reported a mortality of 3.4% in one of his series [1].

Successful management is aimed at early diagnosis and stabilization, following which prompt delivery is desirable in the presence of the following: evidence of worsening pre-eclampsia such as increasing arterial pressure, cerebral symptoms and signs, worsening hepatic or renal function or severe thrombocytopenia; gestational age at or beyond 32–34 weeks; evidence of fetal distress; evidence of fetal maturity [6]. In the majority of cases, the condition tends to resolve soon after delivery. For obstetric reasons, Caesarean section rates are high: Thiagarajah and colleagues reported an incidence of 61.5% [6], whilst Weinstein reported 76% [1]. Many of these patients present for emergency Caesarean section with little or no warning to the anaesthetist and this may allow only a limited time for investigations.

Preoperative haematological investigations should include platelet count, white blood cell count, PCV, partial thromboplastin time, fibrinogen concentration, fibrin degradation products, peripheral blood smear, liver function tests and serum concentrations of creatinine, urea and uric acid [6]. A chest x-ray should be obtained to exclude early pulmonary oedema and ECG examination performed. Platelet transfusion has been recommended if the platelet count is less than 50000 mm$^{-3}$ in patients for Caesarean section and less than 20000 mm$^{-3}$ in patients to be delivered vaginally [3]. A transfusion of fresh whole blood is recommended if the haemoglobin concentration is less than 10 g% [3]. A urinary catheter should be passed for hourly monitoring of urinary output. If the output is low and a diagnosis of acute renal failure is considered, measurement of urine concentrations of sodium and osmolality may be useful in confirming a diagnosis and directing treatment. A balloon-tipped pulmonary artery catheter or central venous catheter is indicated in critically ill patients for fluid management. This avoids hypotension at induction of anaesthesia, as many of these patients are relatively hypovolaemic. Measurement of maternal acid–base status is indicated in patients with clinical or radiological evidence of pulmonary complications or with a coagulation disturbance [3]. Maternal blood glucose concentration should be measured during operation, as severe hypoglycaemia has been reported in association with HELLP syndrome [7]. Many of these patients may be receiving therapy to control arterial pressure; i.v. magnesium sulphate or hydralazine have been used successfully for this purpose [6].

The choice of anaesthetic technique depends on the individual anaesthetist. The use of regional techniques may be limited by the coagulation disturbance and the urgency of the situation in the presence of fetal distress. Thiagarajah and colleagues reported successful use of extradural anaesthesia in a patient with HELLP syndrome, although the platelet count at the time of operation was 112000 mm$^{-3}$ [6]. In view of the hepatic and renal involvement, anaesthetic drugs with minimal hepatic or renal metabolism should be chosen. Propofol would seem a logical choice for induction of anaesthesia as it has no active metabolites and a short half-life with rapid recovery. Suxamethonium is useful to ensure early good intubating conditions, but its half-life may be prolonged because of decreased serum cholinesterase concentrations as a result of hepatic dysfunction and pregnancy. Neuromuscular block may be maintained with atracurium, which is independent of renal excretion. The choice of volatile agent depends on the individual anaesthetist but, because of its low biotransformation, isoflurane seems a good choice. Intraoperative arterial pressure may be controlled with an infusion of hydralazine and isoflurane. For the first 12 h after operation, patients should be monitored in a high dependency unit where CVP, urinary output and haemodynamic state may be monitored.

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# DELAYED EXCITATORY REACTION FOLLOWING INTERACTION OF COCAINE AND MONOAMINE OXIDASE INHIBITOR (PHENELZINE)

S. G. TORDOFF, J. F. STUBBING AND S. P. K. LINTER

**SUMMARY**

*A case report is presented in which a patient receiving the monoamine oxidase inhibitor, phenelzine, developed a delayed excitatory reaction following administration of topical cocaine spray during anaesthesia for vocal cord surgery. The pharmacological basis of the drug interaction is discussed.*

**KEY WORDS**

*Anaesthetics, local: cocaine. Complications: drug interaction, monamine oxidase inhibitors Pharmacology: cocaine, monoamine oxidase inhibitors.*

Cocaine was introduced into clinical practice by Koller in 1884. It is a surface anaesthetic of the ester type but, because of systemic effects and the danger of causing dependence, its use is currently confined to topical application in anaesthesia for ear, nose and throat surgery [1]. Monoamine oxidase inhibitors (MAOI) are a group of drugs used in the management of depression, and are known to interact with many drugs used in anaesthetic practice. A case report is presented in which a patient receiving phenelzine medication developed a delayed excitatory reaction following anaesthesia during which topical cocaine spray was administered.

## CASE REPORT

A 66-yr-old man weighing 84 kg presented for a Teflon implant to the left vocal cord. He had undergone left pneumonectomy for carcinoma of the bronchus 3 years earlier, at which time the left recurrent laryngeal nerve had been damaged. He had also undergone two subsequent implant procedures under general anaesthesia without adverse effects. Ten years previously, he had an inguinal hernia repair under general anaesthesia, which had been uneventful. Since the last Teflon implant, he had started medication with phenelzine 15 mg twice daily for depression. He had been taking phenelzine up to the time of surgery.

At the preoperative visit, the patient gave no family history of malignant hyperpyrexia and had no known allergies. Clinical examination revealed no abnormalities, resting arterial pressure was 130/85 mm Hg and heart rate 75 beat $\text{min}^{-1}$. Routine tests showed a plasma potassium concentration of 4.6 mmol $\text{litre}^{-1}$. No premedication was ordered, but the morning dose of phenelzine was administered.

Anaesthesia was induced with thiopentone 500 mg, and muscle paralysis produced with suxamethonium 100 mg and gallamine 8 mg. The vocal cords were sprayed with 1 ml of 10% cocaine spray (as on the two previous implant procedures), and the trachea was intubated with a 5.0-mm microlaryngeal tube. Diazemuls 10 mg was given and anaesthesia maintained with nitrous oxide and 0.5% isoflurane in oxygen. No pethidine or other opioid was administered. The procedure lasted 10 min, during which time arterial pressure remained unchanged and the heart rate regular, with no tachycardia. There was no clinical evidence of muscular rigidity or pyrexia.

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Thirty minutes after completion of the surgery, the patient had regained consciousness and was returned to the ward. He was responding appropriately to commands; heart rate was regular at 80 beat $min^{-1}$, arterial pressure 130/80 mm Hg and ventilatory frequency 16 b.p.m. Thirty minutes after his return to the ward, the patient was discovered by the staff to be unconscious, with generalized coarse tremors and marked muscle rigidity. The heart rate was regular (110 beat $min^{-1}$) and the arterial pressure 110/60 mm Hg. Rectal temperature was 41.5 °C.

He was returned immediately to the recovery room, given 40% oxygen via a Ventimask and cooled using wet blankets and i.v. fluids. Arterial blood-gas analysis showed pH 7.37 (hydrogen ion concentration 42.7), $Pa_{CO_2}$ 5.5 kPa, $Pa_{O_2}$ 19.8 kPa, standard bicarbonate 23.5 mmol $litre^{-1}$ and base excess $-1$ mmol $litre^{-1}$. Blood biochemistry showed sodium 136 mmol $litre^{-1}$, potassium 5.1 mmol $litre^{-1}$ and urea 6.5 mmol $litre^{-1}$.

During the following 30 min the patient's tremor resolved and the temperature decreased to 39.0 °C. Within 7 h he had become fully conscious and orientated, and the core temperature had decreased further to 37.0 °C. Over the next 6 days he remained well, but complained of weakness and generalized muscular pains.

## DISCUSSION

Cocaine potentiates the effects of the catecholamines and the possibility of an adverse drug reaction occurring when cocaine and MAOI are combined is well recognized [2].

Our patient was thought initially to have developed malignant hyperpyrexia, and steps were taken to treat him accordingly. This diagnosis was excluded subsequently as the patient had no family history of the condition, and had previously undergone two similar procedures under general anaesthesia without incident. Blood-gas analysis and serum biochemistry measurements showed no evidence of metabolic acidosis or hypercapnia, and serum potassium concentrations were 5.1 mmol $litre^{-1}$, compared with a preoperative value of 4.6 mmol $litre^{-1}$.

Cocaine toxicity was considered. Cocaine blocks the re-uptake of noradrenaline and exogenous catecholamines and the symptoms and signs are those of sympathetic overactivity. These may be manifest as excitement, anxiety, headache, tachycardia and hypertension, while more severe effects include convulsions and coma. The toxic dose quoted for cocaine in adults ranges from 1.0–1.5 mg $kg^{-1}$ [1] to 3 mg $kg^{-1}$ [3, 4]. The patient weighed 84 kg and received a dose of 100 mg. He had received the same dose on two previous occasions without toxic effects. Cocaine is absorbed rapidly from the trachea, with peak concentrations occurring at 5 min [5], and our patient showed no evidence of toxicity during operation or for 30 min thereafter. It is possible that the delay in the onset of the symptoms was because of the use of thiopentone and diazepam which would both exert a cerebral depressant action, and might mask the clinical features of toxicity in the initial stages. However, the patient recovered full consciousness before being returned to the ward and at this time showed no evidence of sympathetic overactivity.

The MAOI drugs inhibit the enzyme involved in the metabolic breakdown of catecholamines and increase concentrations of amine neurotransmitters. The combination of cocaine and phenelzine could interact to result in a clinical picture of sympathetic stimulation. This synergism would be expected to manifest soon after the administration of the two drugs, but the patient showed no evidence of sympathetic overactivity during operation or for 30 min after operation. In addition, the symptoms of the patient's reaction are not typical of sympathetic overactivity and the time course of their occurrence would exclude this diagnosis.

The interaction of the MAOI with many anaesthetic agents, especially those with the opioids, is well recognized. Stack, Rogers and Linter have reviewed the subject and described two forms of interaction—excitatory and depressive [6]. The excitatory form is characterized by agitation, headache, hyper- or hypotension, muscular rigidity, hyperpyrexia, convulsions and coma. Based on studies in animals, the excitatory reaction typically seen with MAOI and pethidine is thought to be caused by a block of neuronal uptake of cerebral 5-hydroxy tryptamine (5HT) [7, 8], and work in mice linking increasing toxicity of pethidine with increasing concentrations of cerebral 5HT would support this [9]. In a series of animal experiments cocaine was used to augment amine responses to 5HT, and it was noted that cocaine considerably reduced the inactivation of 5HT [10]. It has been suggested also that a critical concentration of 5HT is required to trigger the excitatory form of the reaction [11].

It is possible that our patient experienced an excitatory reaction because of the increased concentrations of 5HT following interaction of cocaine and phenelzine. A critical concentration of 5HT is required to trigger the reaction, which would account for the delay in the onset of the patient's symptoms.

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# EFFECT OF VENTILATION AND CARDIAC OUTPUT ON THE UPTAKE OF ANAESTHETIC AGENTS FROM DIFFERENT BREATHING SYSTEMS: A THEORETICAL STUDY

G. G. LOCKWOOD AND D. C. WHITE

## SUMMARY

*We have investigated the influences of ventilation and cardiac output on uptake of anaesthetic with different breathing systems, by analysis of simple equations and by computer simulation. Increases in cardiac output and ventilation increased uptake from those systems which provided a constant inspired concentration, but not from completely closed systems with the vaporizer out of the circle (VOC), or when using the technique described by Lowe and Ernst. When the vaporizer was inside the circle, uptake increased with ventilation but not with cardiac output. With servo control of end-tidal concentration, uptake increased with cardiac output but not with ventilation. When the fresh gas flow to VOC systems was increased from basal, independence of uptake from ventilation was well maintained until fresh gas flow approached alveolar ventilation, but the independence of uptake from cardiac output was lost much sooner.*

**KEY WORDS**

*Anaesthetic volatile · isoflurane Pharmacokinetics. uptake. Breathing systems*

When drugs are given by mouth, uptake from the gut is known only approximately. Improved control requires parenteral administration because uptake is then equal to the dose administered. Conventional inhalation anaesthesia, using a constant inspired concentration of anaesthetic agent, resembles oral administration in that uptake is unknown. The equivalent of the parenteral route is the completely closed system, in which the quantity of agent vaporized is the dose taken up by the patient (uptake). Although the anaesthetic effect of an inhalation agent is related to its alveolar partial pressure, examination of uptake enables us to understand the influence of physiological variables on anaesthetic alveolar partial pressure. In addition, the total body uptake of inhalation agents is important when considering metabolism and the effects of toxic metabolites.

The importance of ventilation and cardiac output in regulating uptake of anaesthetics from an open system is well understood. However, the influence of breathing system configuration on uptake is not well known. With the increased interest in low flow and closed system anaesthesia, it seems appropriate to examine this question. This paper considers the effects of changes in cardiac output and ventilation on uptake from different breathing systems. We shall consider systems which deliver a constant inspired concentration of anaesthetic, and contrast them with the completely closed circle system. States intermediate between these two extremes are found in clinical practice, and we shall consider these later in this discussion. The second gas effect produces only small variations in uptake, but it is simpler to exclude it from the discussion by considering a single anaesthetic agent in oxygen.

"Constant inspired" systems include Mapleson systems A to E [1] (when the fresh gas flow (FGF) is sufficient), systems using a non-rebreathing

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valve and, in circle systems, the arrangement H of Eger and Ethans [2] (with FGF greater than minute volume—*vide infra*).

By the term "completely closed system" (CCS) we imply a system in which no valve is open to the atmosphere, and FGF matches patient uptake. The CCS can be operated in a number of modes:
(1) Vaporizer outside the circle system (VOC);
(2) Vaporizer inside the circle system (VIC);
(3) the Lowe technique [3];
(4) servo controlled systems [4, 5].
The first two are well known and have been examined in detail for halothane in the classic paper by Mapleson [6]. The Lowe technique involves injection of a fixed dose of anaesthetic (calculated according to body weight and desired alveolar concentration) directly into the system at set times, and is designed to achieve rapidly, and then maintain, that alveolar concentration. Servo controlled systems use measurement of end-tidal anaesthetic concentration for feedback control of anaesthetic injection into the system to reach and maintain a prescribed alveolar anaesthetic concentration.

We use three equations to clarify our discussion. The first is well known and based on the Fick principle:

$$U_{\mathrm{B}} = (P\mathrm{a}-P\bar{\mathrm{v}}).\dot{Q}.\lambda_{\mathrm{B/G}} \qquad (1)$$

where $U_{\mathrm{B}}$ = rate of uptake of vapour into blood (ml min$^{-1}$); $P\mathrm{a}$, $P\bar{\mathrm{v}}$ = partial pressures of anaesthetic in arterial blood and in mixed venous blood (expressed as a fraction of ambient pressure), respectively; $\dot{Q}$ = cardiac output (ml min$^{-1}$); $\lambda_{\mathrm{B/G}}$ = blood/gas partition coefficient.

Similarly, if we neglect the difference between inspired and expired volumes, we have:

$$U_{\mathrm{L}} = (P\mathrm{I}-P\mathrm{A}).\dot{V}\mathrm{A} \qquad (2)$$

where $U_{\mathrm{L}}$ = rate of uptake of vapour into the lungs from the breathing system (ml min$^{-1}$); $P\mathrm{I}$, $P\mathrm{A}$ = inspired and alveolar partial pressures of anaesthetic (expressed as a fraction of ambient pressure), respectively; $\dot{V}\mathrm{A}$ = alveolar ventilation (ml min$^{-1}$).

The difference between $U_{\mathrm{L}}$ and $U_{\mathrm{B}}$ is the rate of change of volume of anaesthetic vapour in the functional residual capacity (FRC) and dissolved in lung tissue, and so is proportional to the rate of change of $P\mathrm{A}$. Except for the period of washin into the FRC after a change of anaesthetic concentration in the fresh gas flow, this difference is small relative to the values of $U_{\mathrm{L}}$ and $U_{\mathrm{B}}$ themselves, and we neglect it here. Thus we can solve (2) for $P\mathrm{A}$ and use the resulting expression as an approximation for $P\mathrm{a}$ in (1) [7]. Re-arranging, we obtain:

$$\text{Rate of uptake} = \frac{P\mathrm{I}-P\bar{\mathrm{v}}}{\dfrac{1}{\dot{Q}.\lambda_{\mathrm{B/G}}}+\dfrac{1}{\dot{V}\mathrm{A}}} \qquad (3)$$

It follows from (3) that rate of uptake increases with inspired concentration of anaesthetic. Under normal circumstances we have little knowledge of $P\bar{\mathrm{v}}$, even though it is of such importance in determining uptake. For the purposes of our discussion, we can say that any effect cardiac output and ventilation may have on uptake is greatest when $(P\mathrm{I}-P\bar{\mathrm{v}})$ is maximal—that is, at the start of the anaesthetic or after the inspired concentration is increased.

Equation (3) gives us the effect of cardiac output, blood/gas partition coefficient and alveolar ventilation on uptake for given values of $P\mathrm{I}$ and $P\bar{\mathrm{v}}$. Furthermore, we see that when the value of either $\dot{V}\mathrm{A}$ or $\dot{Q}.\lambda_{\mathrm{B/G}}$ is small, the effect produced by changes in the other is diminished. Consequently, uptake of an agent may be ventilation-limited or perfusion-limited. In particular, use of agents with a low blood/gas partition coefficient (e.g. nitrous oxide, desflurane or sevoflurane) ensures that uptake of the agent is perfusion-limited, and therefore little influenced by changes in ventilation.

Conclusions drawn from these equations are qualitative in nature because there is no simple method of estimating $P\bar{\mathrm{v}}$. We have used a computer program (Narkup—see Appendix) to simulate patient uptake from different breathing systems [8]. Data from this program have been used to produce the graphs which illustrate the points made in this paper by showing cumulative uptake of liquid anaesthetic.

We stress that we are discussing anaesthetic uptake, not the change in alveolar concentration with which most anaesthetists are more familiar. To emphasize the difference, consider induction of anaesthesia using an open system. Increased cardiac output slows the increase in alveolar concentration of an anaesthetic agent, but increases its uptake (*vide infra*). On the other hand, increased ventilation increases both the uptake and the rate of increase of alveolar concentration.

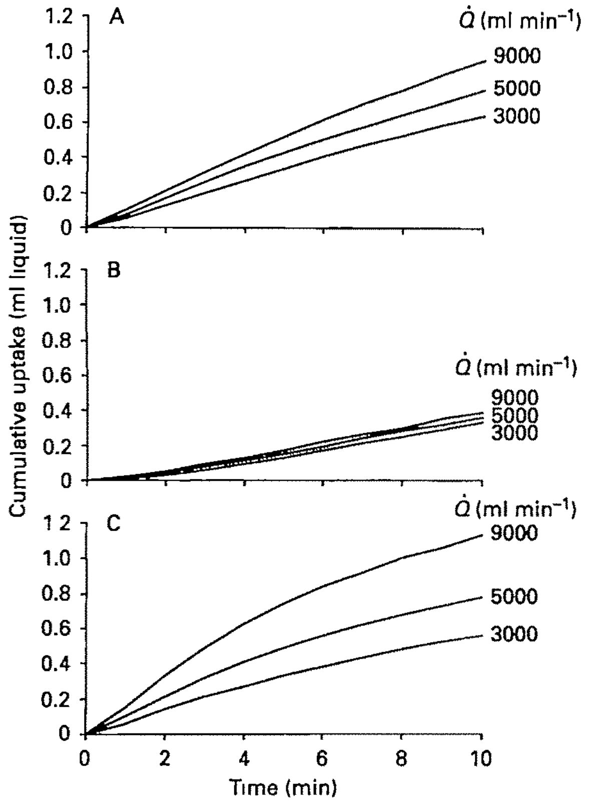

FIG. 1. Cumulative uptake of isoflurane from different breathing systems at three fixed values of cardiac output. A: Constant inspired concentration of 1%. B: VOC (FGF 200 ml min$^{-1}$, vaporizer set to 5%. VIC and Lowe techniques are similar.) C: Servo controlled system with target end-tidal concentration 0.5%. All for 70-kg patient, minute volume 5500 ml min$^{-1}$, deadspace/tidal volume ratio 0.35. Data for all curves generated by Narkup—see Appendix.

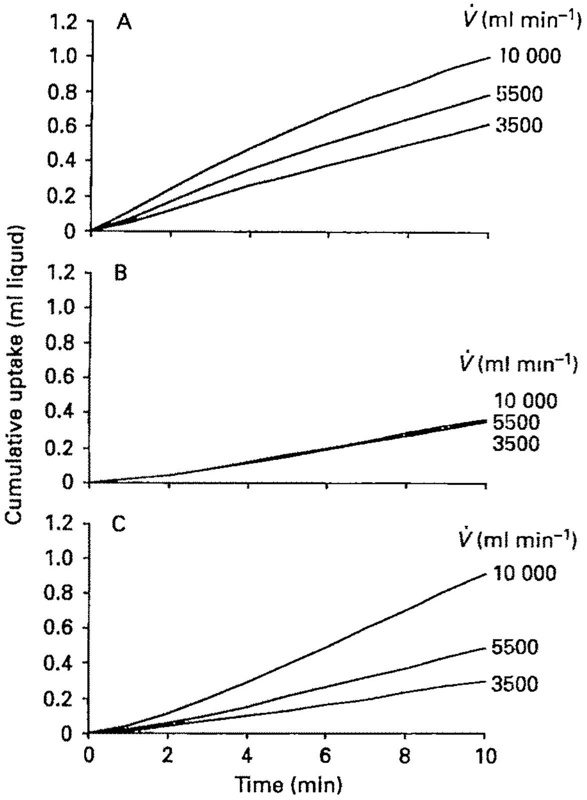

FIG. 2. Cumulative uptake of isoflurane from different breathing systems at three minute volumes. A: Constant inspired concentration of 1%. B: VOC (FGF 200 ml min$^{-1}$, vaporizer set to 5%. Lowe technique and servo controlled systems are similar.) C: VIC (FGF 200 ml min$^{-1}$, vaporizer set to 0.3%). All for 70-kg patient, cardiac output fixed at 5000 ml min$^{-1}$ and a deadspace/tidal volume ratio of 0.35. Data for all curves generated by Narkup—see Appendix

### CONSTANT INSPIRED CONCENTRATION SYSTEMS

Equation (3) describes the effect of cardiac output on uptake when the inspired concentration is held constant—the rate of uptake increases with cardiac output (fig. 1A). Hypoventilation attenuates this response.

We also see from (3) that uptake increases with ventilation (fig. 2A), but that this effect is seen less well when cardiac output is depressed or solubility is low (because uptake is perfusion-limited).

### COMPLETELY CLOSED SYSTEMS

#### *Vaporizer outside the circle*

The situation changes when $P_I$ is no longer held constant. Consider a VOC system with a fixed concentration of anaesthetic entering the system in the basal FGF. Effectively, the whole system of patient and CCS is receiving an infusion of anaesthetic at a constant rate. If, for any reason, rate of uptake by the patient decreases, the balance of the anaesthetic infusion increases the concentration within the breathing system. Equation (3) predicts that this has the effect of restoring uptake, at least to some extent. Similarly, if uptake increases, inspired concentration must decrease, thus slowing uptake. At first sight, it is remarkable that this effect of uptake on inspired concentration produces almost perfect compensation for those factors affecting uptake (figs 1B, 2B), but it is a simple consequence of the fact that the system is completely closed.

Consider the case when uptake is reduced, from any cause. Unless this reduction is catastrophic (apnoea or circulatory arrest), it follows from (3) that it is possible to overcome it by a sufficient increase in inspired concentration. Provided oxygen uptake is maintained and the system remains closed, the excess anaesthetic flowing into the system produces an increase in inspired concentration limited only by the saturation vapour pressure of the agent, so there is the potential for very large increases in inspired concentration of an agent such as halothane or isoflurane. (It has been accepted hitherto that the concentration of anaesthetic within a completely closed circle system with VOC does not increase to more than that in the fresh gas [9]. In practice, this is substantially true for agents such as halothane, but may not be true for new agents of lesser blood solubility. We expect the concentration of desflurane within the circle often to be greater than in the fresh gas.) Under the circumstances described (reduction of uptake from any cause) the inspired concentration increases until a new balance is attained, with the inspired concentration just sufficient to drive anaesthetic into blood at a rate equal to the infusion of agent into the system.

This implies that uptake from a CCS with VOC is independent of cardiac output and of ventilation.

### *Vaporizer inside the circle*

When the vaporizer is in the circle, anaesthetic is vaporized approximately in proportion to minute volume. If ventilation is held constant, a VIC system is functionally identical to a VOC system, and so uptake is not affected by changes in cardiac output (fig. 1B). However, because vaporization is proportional to minute volume, an increase in ventilation increases the concentration of anaesthetic within the system. We conclude from equation (3) that, with the vaporizer inside the circle, uptake increases with ventilation (fig. 2C).

### *The Lowe technique*

Although this technique actually involves the injection of liquid anaesthetic into the system, we may consider it as a special form of VOC for the purposes of our discussion (that the vaporizer would have to produce supersaturated vapour does not effect our arguments). The injected doses (analogous to vaporizer setting multiplied by volume of fresh gas since last dose) are predetermined and independent of ventilation and of cardiac output, so that the system is functionally equivalent to a VOC system. Thus, when Lowe's technique is used, uptake of anaesthetic is not affected by changes in ventilation or cardiac output (figs. 1B, 2B).

TABLE I. *Summary—effect of ventilation and cardiac output on uptake from different breathing systems*

| System | Increase in Ventilation | Increase in Cardiac output |
|---|---|---|
| Open | + | + |
| VOC | 0 | 0 |
| VIC | ++ | 0 |
| Lowe | 0 | 0 |
| Servo | 0 | ++ |

### *Servo controlled systems*

These systems (described above) maintain a constant alveolar concentration and cannot be simulated conveniently by a VOC system, but their functional characteristics are deduced easily from equation (1).

In this equation, ventilation does not appear explicitly. However, we use $P_A$ as an estimate of $P_a$, and $P_A$ may depend on ventilation. Servo controlled systems hold $P_A$ constant so that, in this case, equation (1) suggests that uptake is independent of ventilation (fig. 2B). Furthermore, we see that uptake is directly proportional to cardiac output and blood/gas partition coefficient. With this system, uptake is affected more by changes in cardiac output than is the case for the constant inspired systems (fig. 1C, A, respectively).

The changes shown in figures 1 and 2 are summarized in table I.

## TRANSITIONAL STATES: OPENING THE CLOSED SYSTEM

What happens to the functional characteristics of the circle system as FGF is increased from basal requirements to the minute volume or more? These conditions are more difficult to analyse than the two cases (constant inspired and CCS) described, in which one of the factors controlling uptake is fixed. We have therefore relied exclusively on our computer model of uptake and distribution (see Appendix). The breathing sys-

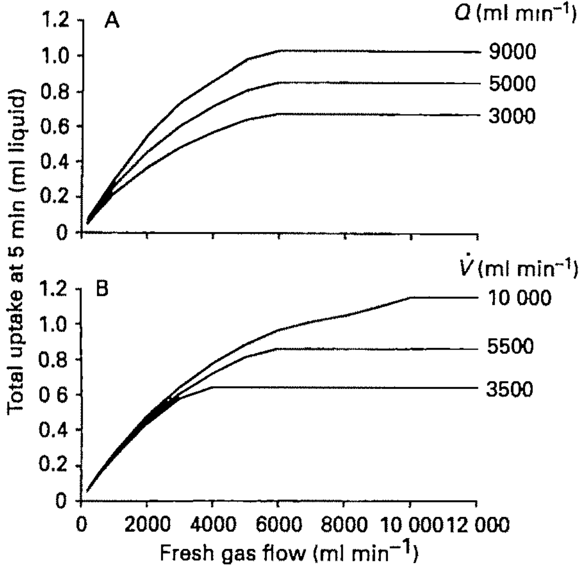

FIG. 3. Effect of cardiac output and ventilation on rate of uptake of isoflurane as fresh gas flow increases A: Three values of cardiac output, minute volume constant at 5500 ml min$^{-1}$. B: Three values of minute volume, cardiac output constant at 5000 ml min$^{-1}$. All for 70-kg patient, arrangement H of circle system, vaporizer out of circle and set to 2 %, deadspace/tidal volume ratio 0.35 All data generated by Narkup—see Appendix.

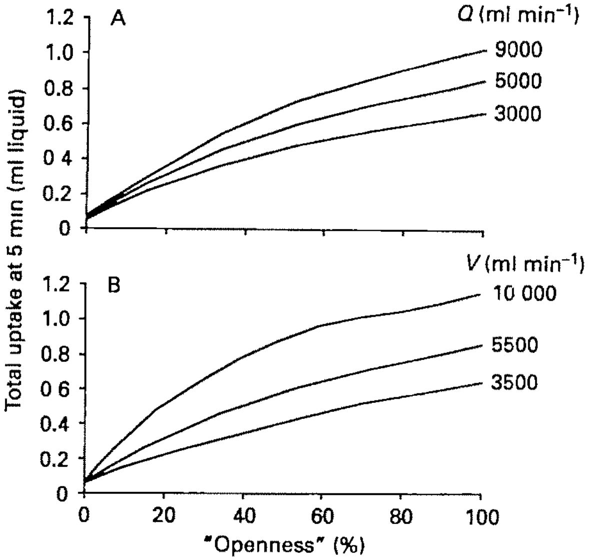

FIG. 4. Effect of cardiac output and ventilation on rate of uptake of isoflurane as system openness increases. A: Three values of cardiac output, minute volume constant at 5500 ml min$^{-1}$. B: Three values of minute volume, cardiac output constant at 5000 ml min$^{-1}$. All for 70-kg patient, arrangement H of circle system, vaporizer out of circle and set to 2 %, deadspace/tidal volume ratio 0.35. All data generated by Narkup—see Appendix. See text for definition of openness.

tem we consider is the H arrangement of the circle system [2], which is characterized ideally by absence of rebreathing of alveolar gas when FGF equals or exceeds the alveolar ventilation; that is, when the FGF equals alveolar ventilation, the soda-lime canister is unnecessary. This characteristic holds for both spontaneous and controlled ventilation. When FGF equals alveolar ventilation, some of the inspired gas must come from the circle reservoir. The circle configuration is such that some of this gas must be inspired into the alveoli, so the inspired isoflurane concentration does not equal that in the fresh gas at this rate of flow. We have assumed that the inspired gas comprises only fresh gas when FGF equals (or is greater than) the minute volume, and is otherwise a perfect mix of fresh and circle gas.

The results of these investigations are shown in figure 3. As FGF increases from basal, thus opening the system, the effect of cardiac output on uptake becomes gradually more important (fig. 3A). In contrast, ventilation has negligible effect on uptake until FGF exceeds 3000 ml min$^{-1}$ (fig. 3B). The reason for this difference is that the degree of "openness" of the system depends not only upon FGF, but also on minute volume. Because we have assumed that $P_I$ is constant when the FGF is greater than or equal to the minute volume, we can quantify openness in the following simple way:

$$\text{openness} = \frac{\text{minimum (FGF, minute volume)} - \text{basal flow}}{\text{minute volume} - \text{basal flow}} \times 100\,\%$$

Thus a CCS is 0 % open and, for a given minute volume, the percentage openness increases linearly with FGF, to a maximum value of 100 % when FGF is sufficient to ensure a constant inspired concentration.

If the curves in figure 3 are redrawn using openness as the horizontal axis, the effects of both cardiac output (fig. 4A) and ventilation (fig. 4B) are seen to increase evenly as the system is opened.

Do these findings have any practical significance? It might be considered undesirable that a system maintain uptake in the face of decreasing cardiac output, for this would imply that, if the patient's circulation was impaired by any cause (e.g. blood loss, excessively deep anaesthesia), then alveolar concentration would increase and further embarrass cardiac output. This is contrary to clinical practice—the anaesthetist normally reduces the inspired concentration when these conditions occur. The only systems in which rate of uptake is reduced automatically by decreasing cardiac output are the constant inspired systems, and servo controlled systems (fig. 1A, C).

Reduced ventilation in a spontaneously breathing patient is a sign that anaesthesia is too deep in relation to surgical stimulation. The constant inspired and the VIC systems are self-regulatory in this respect (fig. 2A, C). This may be advantageous.

The findings presented in figure 3B suggest that, in a low flow circle system (e.g. FGF less than 3000 ml $min^{-1}$), an increase in ventilation does not increase uptake because the larger minute volume renders the system functionally less open. However, the data for figures 3 and 4 are derived from a computer simulation based on an idealized breathing system and an idealized patient. They await experimental verification.

## APPENDIX

Our computer program Narkup models the H arrangement of the circle system [2]. It is assumed that the circle has an initial volume of 5000 ml, a maximum volume of 6000 ml (after which gas is expelled through the pop-off valve, with preferential loss of alveolar gas), that it contains 100% oxygen at the start of the anaesthetic, and that no isoflurane is lost into rubber and plastic components. The model assumes that inspired gas is composed of fresh gas, supplemented by gas from the circle—these are mixed perfectly before being inspired. Expired gas which is not vented from the system is assumed to mix perfectly with existing circle gas.

The patient is based on Eger's four-compartment patient model [10], with the addition of a peripheral shunt. We use physiological data taken from those given by Davis and Mapleson [11]. Mathematical modelling is simplified by assuming "continuous alveolar ventilation"—it is assumed that inspired gas enters the alveoli continuously, and that, simultaneously, alveolar gas is being expired at a rate that maintains a constant FRC in the face of uptake. Gas within the alveoli is always a perfect mixture. Although a mechanical analogue of this would require separate inflow and outflow pipes to and from a mixing chamber, nonetheless we have adopted it because it is computationally so convenient.

Physico-chemical properties of isoflurane are given by Fischerova-Bergerova [12] and by Lowe and Ernst [3]. The values used in the program are shown in table II.

TABLE II. *Physiological and physico-chemical values assumed by Narkup. CO = Cardiac output. Note: 50% of the blood volume, divided into four parts in proportion to the compartment bulks, has been added to those compartments, giving slightly larger values for volume than in the reference [11]. We neglect the error introduced by assuming this blood to have the same affinity for anaesthetics as the tissues. Of the remaining 50% of the blood volume, 33% is assumed to be in the arterial system, and 67% in the venous*

| Tissue | Volume (litres) | Blood flow (% of CO) | $\lambda_{T/G}$ | $\lambda_{T/B}$ |
|---|---|---|---|---|
| Blood | 5.5 | | 1.4 | |
| Vessel rich group | 5.4 | 61.8 | | 2.3 |
| Muscle group | 38.6 | 17.7 | | 1.7 |
| Vessel poor group | 6.2 | 0.2 | | 2.3 |
| Fat | 16.5 | 5.3 | | 49 |
| Lung | 0.5 | | 1.6 | |
| Shunt | | | | |
| Left-to-right | | 15 | | |
| Right-to-left | | 5 | | |

The algorithm presented below is repeated every 10 s of model time. It starts with known values for various variables (e.g. alveolar partial pressure of isoflurane is zero initially) and calculates how those values change in the next 10 s. The new values are then used to project a further 10 s, and so on. Mathematically, this is a process of interdependent integrations and the best numerical solution would take this interdependence into account. The implementation of such an approach would be extremely time consuming, with no clinically significant improvement of accuracy, and would be inappropriate for a model with so many arbitrary assumptions. We have adopted a simpler approach, using a classical fourth-order Runge-Kutta technique to solve the equations for alveolar, arterial and tissue isoflurane partial pressures (which empirical testing has shown to be the most critical), but cruder integration techniques elsewhere.

In the following, $P_I$, $P_A$ and $P_{\bar{v}}$ denote the inspired, alveolar and mixed venous isoflurane partial pressures, respectively. All partial pressures are understood to be expressed as fractions of the ambient pressure, all volumes are in ml and all flows are ml $min^{-1}$. The program automatically augments the fresh gas flow to allow for vaporized agent, but no temperature corrections are made.

*Step 1.* The minute volume, $\dot{V}$, comprises the fresh gas flow supplemented, if necessary, by rebreathed gas from the circle. It is divided into deadspace ventilation, $\dot{V}_D$ and the inspired alveolar ventilation $\dot{V}_{A,I}$ in the proportion 35:65. When a constant inspired concentration system is used, the inspired concentration is simply the concentration in the fresh gas. When using VOC, the inspired isoflurane concentration is calculated as follows:

$$P_I = \frac{\text{minimum}\ (\dot{V}, \text{FGF})\ P_{FGF} + \text{maximum}\ (\dot{V} - \text{FGF}, 0)\ P_{circle}}{\dot{V}}$$

where $P_{FGF}$, $P_{circle}$ = concentration of isoflurane in the fresh gas flow and in the reservoir of the circle system, respectively.

For VIC, the vaporizer is assumed to be on the inspiratory limb, and it is calibrated so that when set to 1 % it increases the ***halothane*** concentration of the gas passing over it by 1 %. To accommodate other agents, we assume that the rate of liquid vaporization is unchanged between agents, but because 1 ml of liquid isoflurane produces less vapour than 1 ml of liquid halothane, there is a small reduction in the output concentration. Thus.

$$P_\mathrm{I} = \frac{P\mathrm{circle} \cdot \mathrm{maximum}\ (\dot{V} - \mathrm{FGF},\ 0) + P\mathrm{vap} \cdot \dot{V} \cdot \frac{206}{240}}{\dot{V}}$$

where $P\mathrm{vap}$ = vaporizer setting.

*Step 2*. The expired alveolar ventilation is calculated.

$$\dot{V}_{\mathrm{A,E}} = \dot{V}_{\mathrm{A,I}} \cdot \mathrm{factor} - (U_\mathrm{B} + \dot{V}_{\mathrm{O}_2}\ (1 - RQ))$$

$$\mathrm{factor} = 1 + P_{\mathrm{A}_{\mathrm{H_2O}}} \left( \frac{\mathrm{minimum}\ (\dot{V},\ \mathrm{FGF})}{\dot{V}} \right)$$

where $\dot{V}_{\mathrm{A,E}}$, $\dot{V}_{\mathrm{A,I}}$ = inspired and expired alveolar ventilations, respectively; "factor" increases the volume of the inspired gas to allow for the vaporization of water needed to humidify the non-rebreathed gas (assuming that fresh gas is dry, rebreathed gas is saturated and $P_{\mathrm{A}_{\mathrm{H_2O}}} = 0.06$); $U_\mathrm{B}$ = flow of isoflurane vapour into the blood (and so is negative during eduction). This starts at zero and is recalculated repeatedly in step 7 on every cycle through the algorithm; $\dot{V}_{\mathrm{O}_2} \cdot (1 - RQ)$ = difference between oxygen consumption and carbon dioxide production. The program assumes a constant oxygen uptake of 214 ml $\mathrm{min}^{-1}$ and a respiratory quotient of 0.82 in the examples used here.

Thus the model of ventilation is of constant flow of inspired gas into the FRC, instant mixing there, and constant efflux of gas from the FRC at a rate which maintains a constant FRC.

*Step 3*. The alveolar isoflurane partial pressure, $P_\mathrm{A}$, is calculated using:

$$\frac{\mathrm{d}}{\mathrm{d}t} P_\mathrm{A} = \frac{P_\mathrm{I} \cdot \dot{V}_{\mathrm{A,I}} + P_{\bar{\mathrm{v}}} \cdot \dot{Q}\mathrm{pulm} \cdot \lambda_{\mathrm{B/G}} - P_\mathrm{A}\ (\dot{V}_{\mathrm{A,E}} + \dot{Q}\mathrm{pulm} \cdot \lambda_{\mathrm{B/G}})}{\mathrm{FRC} + V_\mathrm{L} \cdot \lambda_{\mathrm{L/G}}}$$

where $\dot{Q}\mathrm{pulm}$ = pulmonary flow; $\lambda_{\mathrm{B/G}}$ = blood/gas partition coefficient for isoflurane; $V_\mathrm{L}$ = lung tissue volume; $\lambda_{\mathrm{L/G}}$ = lung/gas partition coefficient for isoflurane. It is assumed that lung tissue is always in equilibrium with alveolar gas, and so $V_\mathrm{L} \cdot \lambda_{\mathrm{L/G}}$ is added to the FRC when dividing the rate of change of volume of agent to give the rate of change of alveolar concentration. The volume of the FRC is taken to be 2500 ml.

The equation is derived from (1) and (2) in the main text, with corrections made for the difference between inspired and expired volumes, and for the absorption of isoflurane directly into lung tissue.

*Step 4*. New values for the volume and composition of circle gas are calculated. First, a volume of gas equal to one-sixth of the rebreathed flow (i.e. 10 seconds-worth) is subtracted from the circle volume $V\mathrm{circle}$. If FGF is greater than minute volume, the excess is ignored. The reduced circle volume is denoted $V^{-}\mathrm{circle}$. This does not imply inspiration: as stated above, flow in and out of the alveoli is assumed to be continuous and simultaneous. We are merely forming a new set of approximations every 10 s.

$$V^{-}\mathrm{circle} = V\mathrm{circle} - \frac{\mathrm{maximum}(\dot{V} - \mathrm{FGF},\ 0)}{6}$$

The deadspace gas and the expired alveolar gas are added to the circle, ensuring that the circle volume does not increase to more than 6 litre (alveolar gas is wasted preferentially). Carbon dioxide is then absorbed:

$$V\mathrm{circle} = V^{-}\mathrm{circle} + V_{\mathrm{D}_{\mathrm{recirc}}} + (1 - P_{\mathrm{A}_{\mathrm{CO_2}}}) \cdot V_{\mathrm{A}_{\mathrm{recirc}}}$$

$$V_{\mathrm{D}_{\mathrm{recirc}}} = \mathrm{minimum} \left( \frac{\dot{V}_\mathrm{D}}{6},\ 6000 - V^{-}\mathrm{circle} \right)$$

$$V_{\mathrm{A}_{\mathrm{recirc}}} = \mathrm{minimum} \left( \frac{\dot{V}_{\mathrm{A,E}}}{6},\ 6000 - (V^{-}\mathrm{circle} + V_{\mathrm{D}_{\mathrm{recirc}}}) \right)$$

The new partial pressure of isoflurane within the bulk of the breathing system can now be calculated:

$$P\mathrm{circle} = \frac{P'\mathrm{circle} \cdot V^{-}\mathrm{circle} + P_\mathrm{I} \cdot V_{\mathrm{D}_{\mathrm{recirc}}} + P_\mathrm{A} \cdot V_{\mathrm{A}_{\mathrm{recirc}}}}{V\mathrm{circle}}$$

where $P'\mathrm{circle}$ = last calculated (or assumed) value of partial pressure of isoflurane within the circle.

*Step 5*. The arterial partial pressure of isoflurane is calculated, using the current value of right-to-left shunt and assuming that the mixed venous partial pressure is constant for the 10-s period. The calculation is based on:

$$\frac{\mathrm{d}}{\mathrm{d}t} P\mathrm{a} = \frac{\dot{Q}\mathrm{pulm}}{\dot{Q}} \ \frac{\mathrm{d}}{\mathrm{d}t} P_\mathrm{A}$$

Anaesthetic is stored in the blood for 10 model seconds to simulate delay in transport to the tissues.

*Step 6*. Calculate the partial pressure of isoflurane in the tissue compartments, $P\mathrm{tiss}$:

$$\frac{\mathrm{d}}{\mathrm{d}t} P\mathrm{tiss} = \frac{(P\mathrm{a} - P\mathrm{tiss}) \cdot \dot{Q}\mathrm{tiss}}{V\mathrm{tiss} \cdot \lambda_{\mathrm{T/B}}}$$

where $\dot{Q}\mathrm{tiss}$ = tissue blood flow; $V\mathrm{tiss}$ = tissue volume; $\lambda_{\mathrm{T/B}}$ = tissue/blood partition coefficient for isoflurane.

*Step 7*. Calculate rate of uptake from the lungs, $U_\mathrm{B}$, and total uptake from the lungs, of isoflurane (note that agent trapped in the FRC and lung tissue is not included in this definition of uptake):

$$U_\mathrm{B} = (\overline{P_\mathrm{A}} - P_{\bar{\mathrm{v}}}) \cdot \dot{Q}\mathrm{pulm} \cdot \lambda_{\mathrm{B/G}}$$

where $\overline{P_\mathrm{A}}$ = average of last and current estimate of $P_\mathrm{A}$.

The rate of uptake is assumed constant over the 10-s interval, so the amount of uptake is simply the product of the rate of uptake and the 10-s time interval. Cumulative uptake is obtained by summing these small amounts, and this is the result used in the figures. It can be compared to the sum of the anaesthetic content of the four tissue compartments, and of the blood. The differences between the two values—which is a reflection of the accuracy of the numerical work—is never of clinical significance

*Step 8*. Calculate the mixed venous isoflurane partial pressure by taking the average for the tissue compartments, weighted by their blood flows:

$$P_{\bar{\mathrm{v}}} = \frac{\sum P\mathrm{tiss} \cdot \dot{Q}\mathrm{tiss}}{\dot{Q}}$$

where $\dot{Q}\mathrm{tiss}$ and $\dot{Q}$ = blood flow through the tissue compartment and total cardiac output, respectively. The sum is taken over five tissue compartments—Eger's four, and a fifth representing the peripheral shunt. The result is stored internally for 20 model seconds to simulate delay in the circulation, and the value used as the "next $P_{\bar{\mathrm{v}}}$" is the result calculated 20 model seconds ago.

*Step 9.* Start again at step 1.

The results obtained match equation (3) closely if predicted values of $P\bar{v}$ are used, and are also in accord with clinical data obtained from the Northwick Park Hospital servo controlled anaesthetic machine [13], and with data given by Lowe and Ernst [3].

Narkup can perform similar calculations for halothane, enflurane, sevoflurane, desflurane, cyclopropane and xenon, all with or without nitrous oxide. The nitrous oxide calculations are made in parallel with those for the other agent, allowing demonstration of the second gas effect. The program can model depression of ventilation and cardiac output by volatile agents, according to data given by Eger [14]. The age and weight of the patient, and the relative size and perfusion of the tissue compartments can all be varied. Results are presented in graphical and numerical form, and some effort has been made to make the program user-friendly. We are prepared to distribute copies to readers who request them.

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*British Journal of Anaesthesia* 1991; **66**: 527–530

# CORRESPONDENCE

## PHARMACOKINETICS OF PROPOFOL

Sir,—We read with interest the pharmacokinetic study of a propofol infusion during cardiac surgery by Massey and colleagues [1].

It is illogical to infuse propofol *after* induction of anaesthesia at a constant rate of 4 mg kg$^{-1}$ h$^{-1}$ during which the desired blood concentration of greater than 1 μg ml$^{-1}$ is not achieved until approximately 10–15 min. While it is debatable that 1 μg ml$^{-1}$ is sufficient to produce anaesthesia, we believe that it is not acceptable to achieve this as late as 10 min after induction and intubation.

It would seem more appropriate either to give an initial bolus dose and start the propofol infusion simultaneously, or to start the constant infusion before induction. Although an induction dose of propofol 2.5 mg kg$^{-1}$ is associated with hypotension [2], a reduced dose, given slowly, is less likely to cause haemodynamic instability [3].

Using a computer model [4] we have calculated that the bolus dose should be 0.4 mg kg$^{-1}$, with an infusion of 4 mg kg$^{-1}$ h$^{-1}$. The rapidity with which a calculated blood concentration of propofol exceeds 1 μg ml$^{-1}$ is shown in figure 1. Also demonstrated is the considerable delay, using Massey's regimen, in achieving the concentration of propofol required to guarantee hypnosis.

In addition, the dose of midazolam used at induction (0.03 mg kg$^{-1}$) does seem inappropriately small (a maximum of 3 mg in a patient of 127 kg) and, although there were no reports of awareness on direct questioning, with the small number of patients in their study, this may reflect a lack of recall rather than awareness *per se*.

We feel that, with the procedure as described, patients are at risk of awareness during the first 15 min, especially with a technique that did not involve nitrous oxide. A recent editorial [5] has cautioned us to be prudent with new methods of anaesthesia, and one such as this may bring the technique of i.v. anaesthesia rapidly into disrepute.

V. S. Sidhu
G. de L. Dear
R. M. Grounds
*London*

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Sir,—Thank you for giving us the opportunity to respond to the comments in this letter.

It is not only debatable, but is unlikely that a blood concentration of propofol 1 μg ml$^{-1}$ alone provides anaesthesia, especially for patients undergoing open heart surgery. In this context, we were using propofol as a hypnotic. We consider that our use of propofol following induction of hypnosis is not illogical, but is analogous to the use of gaseous agents following i.v. induction agents.

In our anaesthetic regimen, analgesia was provided by premedication including papaveretum i.m. (20 mg in seven patients, 15 mg in three patients) according to sex and weight and alfentanil i.v. to a total dose of 100 μg kg$^{-1}$ plus 60 μg kg$^{-1}$ h$^{-1}$.

Hypnosis was induced by the sedative effects of premedication and midazolam i.v. according to patient response (3 mg in eight patients, 2.5 mg in two patients). Ninety seconds after midazolam, all patients were unresponsive to command and to manual inflation of the lungs using a mask circuit. Hypnosis was then maintained using the propofol infusion.

The discussion of Dr Sidhu and colleagues relates to whether i.v. propofol 0.4 mg kg$^{-1}$ (approx. 30 mg) followed by an infusion of 4 mg kg$^{-1}$ h$^{-1}$ provides more reliable hypnosis than a hypnotic dose of midazolam i.v. followed by an infusion of propofol 4 mg kg$^{-1}$ h$^{-1}$ in the presence of full opioid analgesia. This cannot be answered by either measuring or computing drug concentrations in the blood, as the sedative effects of the opioids and hypnotics used are cumulative

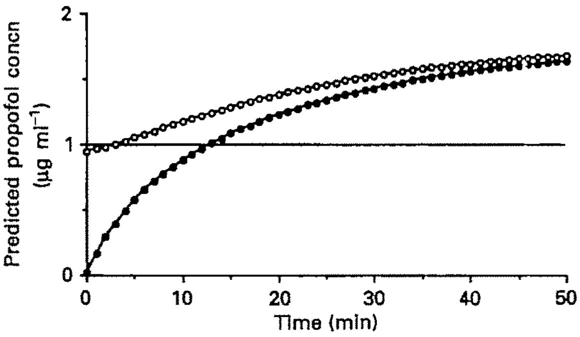

Fig. 1. Changes in predicted blood concentration of propofol following infusion of 4 mg kg$^{-1}$ h$^{-1}$ (●) and bolus of 0.4 mg kg$^{-1}$ with simultaneous infusion of 4 mg kg$^{-1}$ h$^{-1}$ (○).

Our experience over 4 yr with direct questioning of patients reassures us that hypnosis and haemodynamic stability are provided reliably by the second method. We are currently investigating the dose, and evaluating the haemodynamic effects of propofol for induction and maintenance of hypnosis in the presence of full opioid analgesia in patients undergoing cardiac surgery.

K. Sherry
N J. Massey
*Sheffield*

## EXTRADURAL, SPINAL OR COMBINED BLOCK FOR OBSTETRIC SURGICAL ANAESTHESIA

Sir,—Dr Carrie, in an otherwise excellent review of regional anaesthesia in operative obstetrics [1], dismisses the practice of warming bupivacaine before extradural injection as being inconvenient and hardly merited because of a reduction of block onset time of only 20%. In this respect, he quotes our study [2] which recorded a reduction of 30% in onset time. Moreover, we demonstrated a 23% reduction in volume of local anaesthetic required to achieve satisfactory block, and a significant reduction in the incidence of shivering by injecting bupivacaine warmed previously to body temperature.

Maintaining a small supply of bupivacaine and 20 ml syringes in a thermostatically controlled warming cabinet (a standard fixture in any labour suite or operating theatre) does not impose any measure of inconvenience. There is no necessity to warm any other equipment and we continue to believe that this simple measure significantly improves the technique of extradural anaesthesia for Caesarean section.

D. A. Dutton
J. E. Howie
*Glasgow*

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Sir,—I am grateful for the opportunity to thank Drs Dutton and Howie for their kind remarks about my review article [1] and to comment on the points they raise in their letter.

When discussing the effect of warming local anaesthetic solutions to increase the speed of onset of extradural block, I made reference not only to the work of Dutton and Howie [2], but also to that of Mehta and colleagues [3], whose reduction of onset time of block to T6 was only 21%. A "mean" of the two papers does give a reduction time of 25% so my figure of "about 20%" is only marginally low for the combined results, but underestimates by a few more per cent the 30% reported by Dutton and Howie. I apologize. Their observations on the effect of warming on reduction in volume of local anaesthetic and a reduced incidence of shivering were noted also by Mehta and colleagues, but my comments on the effect of warming were confined to the effect on rate of onset.

What causes me anxiety is their comment about keeping bupivacaine ampoules in a "thermostatically controlled warming cabinet, a standard fixture in any labour suite or operating theatre." Such cabinets do exist, but theatre staff disagree both as to the function of these cabinets and the temperature at which they should be kept. A survey of 11 such cabinets in this district showed a range of temperatures from room temperature (thermostat not functioning) to an alarming 67 °C, with several set at about 50 °C! The consequences of injecting local anaesthetic solution into the extradural space at these greater temperatures might be disastrous. Precise testing of the temperature of the sterile solution is almost impossible, and judgement of temperature through syringes, rubber gloves etc., inaccurate. While temperature is likely to be carefully controlled in the hands of clinicians such as Drs Dutton and Howie, I should feel some trepidation were a wave of enthusiasm for warm bupivacaine to sweep the U.K.!

L. E. S. Carrie
*Oxford*

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## COMPARISON OF DOPAMINE AND DOPEXAMINE

Sir,—The report by Stephan and colleagues [1] comparing the effects of dopexamine and dopamine on cardiovascular and renal haemodynamics gives rise to several areas of concern.

First, the doses of dopexamine and dopamine chosen were not comparable. The authors state that dopexamine has only 33% of the potency of dopamine at $DA_1$ receptors, yet they chose to compare dopexamine 1, 2 and 4 $\mu g\ kg^{-1}\ min^{-1}$ with dopamine 2.5 and 5 $\mu g\ kg^{-1}\ min^{-1}$. Likewise, the dose ranges allow no direct comparison of cardiovascular variables between the groups. Changes in cardiac index and systemic vascular resistance occur with dopexamine at a low dose, whilst dopamine in greater doses does not cause a similar increase in cardiac index and decrease in systemic vascular resistance. Again, this may be predicted from the known receptor pharmacology of these agents. The authors comment on the acceptability of the increase in heart rate seen with dopexamine 4 $\mu g\ kg^{-1}\ min^{-1}$, which resulted also in a 117% increase in cardiac index. We would conclude that, in this population of patients, this dose is unnecessary and excessive.

Second, the authors noted that the increase in renal blood flow was greater than that in cardiac index in those receiving dopamine, the reverse being the case with dopexamine. However, the increase in renal blood flow was not significantly greater with dopamine than with dopexamine, and the decrease in renal vascular resistance was greater with dopexamine.

All patients received calcium channel blockers and some were receiving β-blockers also. There is no comment on which agents were used, the doses, or when the last morning dose was given. This may be relevant for drugs with a long half-life, or if slow-release preparations have been administered. Furthermore, there is little discussion on possible effects of these agents on the results obtained. There is insufficient information to allow us to see how conclusions regarding the pharmacological receptors involved in changes in renal and cardiovascular haemodynamics were derived.

The authors state in the discussion that myocardial ischaemia has been reported with dopexamine, and incorrectly cite the work of Dawson and colleagues [2], who showed no alteration in myocardial oxygen demand or supply with increased rate–pressure products. Although two patients reported mild chest pain with 6 μg kg⁻¹ min⁻¹, there was no ECG evidence of myocardial ischaemia or a greater increase in myocardial oxygen consumption than the group mean. The absence of adverse effects of dopexamine on the myocardium has been observed by others [3]. However, the ST segment depression in this study, shown to occur in patients receiving dopamine [1] and dopexamine [2], emphasizes that caution should be exercised when using inotropic stimulation in patients with coronary artery disease.

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Sir,—We are aware of the fact that equipotent doses of dopexamine and dopamine are difficult to define because of differing receptor activities. This is the reason why we did not perform a statistical comparison between the groups. As we were more interested in renal than in cardiovascular effects of both drugs, we started with dopexamine 1 μg kg⁻¹ min⁻¹ and dopamine 2.5 μg kg⁻¹ min⁻¹ because these doses resulted in comparable increases in renal blood flow. Then we looked at the effects of twice these doses. Our results show clearly that, in contrast with dopamine, dopexamine increased renal blood flow mainly by an increase in cardiac index. Nevertheless, we admit that (as with any other clinical study) we can only speculate on the different receptor potencies of both agents.

We observed that all patients were receiving maintenance doses of calcium channel blocking drugs and that two patients in the dopexamine group and three patients in the dopamine group were treated additionally with β-receptor antagonists. We stated that the last doses of all drugs were administered in the morning of the operation, but omitted to note that these drugs were nifedipine and atenolol. We did not comment on the doses, because oral doses do not allow any conclusions to be drawn on plasma concentrations.

We do not think that we cited the work of Dawson and colleagues incorrectly, because the common surface ECG is not always a sensitive marker of myocardial ischaemia. Berry and colleagues [1] examined the effects of selective regional myocardial ischaemia by occluding vessels during percutaneous coronary angioplasty While ST elevation occurred in 84% of patients during occlusion of the left anterior descending artery and in 92% of patients during occlusion of the right coronary artery, only 32% of patients undergoing occlusion of the left coronary artery demonstrated ST elevation in the routine surface ECG; four of 19 patients of the latter group had only precordial ST depression, and nine (47%!) patients had no ECG changes. Moreover, unaltered global myocardial oxygen consumption does not exclude regional myocardial ischaemia, which can be detected biochemically only by an impaired lactate balance, or even better, by sensitive markers of ischaemia, such as hypoxanthine [2].

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## MEMORY MECHANISMS

Sir,—I read with interest the Editorial in the November issue of the Journal, "Awareness and memory in anaesthetized patients". It contains a short review of memory mechanisms to which I wish to add the following comments.

First, the anatomical basis for memory formation was proposed long before Ramon y Cajal. There is, for example, an account in 1780 by the Italian anatomist Malacarne [1] of an impressive experiment in which he trained one of two siblings of various species (dogs and several birds) and left the other sibling untrained. After a long period, he killed all the animals, examined the brains and reported that there were more folds in the cerebellum of the trained animals than in the untrained ones.

My second comment refers to the absence of any reference to cholinergic mechanisms within the hippocampus (and elsewhere in the forebrain) which mediate memory processes. As anaesthetists, we are very familiar with the effects of hyoscine on memory.

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## USEFULNESS OF PROPOFOL IN TORTICOLLIS

Sir,—Some authors have reported some degree of neuromuscular block associated with the administration of propofol [1], but others were not able to demonstrate any of these properties [2]. Recently, we have demonstrated that propofol is a suitable drug for sedation in patients with tetanus [3]. In particular, we were impressed by the degree of muscular relaxation provided by propofol in this clinical setting. We have administered propofol in two young adults suffering torticollis not relieved by the usual treatment. Clinical manifestations of torticollis are mainly caused by muscular contraction.

The first patient was a woman of 30 yr who suffered for 2 days from torticollis which was not relieved despite chlormezanone 4 × 100 mg and paracetamol 4 × 500 mg orally. Cervical spine x-ray and physical examination were unremarkable, except for tenderness of the neck muscles. She could not turn the head to either side and flexion and extension of the head were limited by pain. She received propofol 2 × 10 mg i.v. at an interval of 5 min. Ten minutes later she had improved and was able to move the head to both sides. Flexion of the head was possible but full extension was still limited by slight pain. Pain on a visual analogue scale decreased from 5 to 2. She was otherwise pain free for the whole day. The following morning, as pain reappeared, she received another bolus of propofol 10 mg i.v. Rapid improvement appeared within 15 min. Degree of sedation was not modified by administration of propofol.

The second patient was a 24-yr-old woman suffering for 3 days from torticollis. Cervical spine x-ray and physical examination were unremarkable. Moving the head to the left was impossible. No improvement was noticed despite chlormezanone 4 × 100 mg $day^{-1}$ orally and mefanimic acid 3 × 250 mg $day^{-1}$ orally. The patient received propofol 10 mg i.v. and, within 5 min, she felt improved, but still had some difficulty in turning the head to the left. She received a second dose of propofol 10 mg i.v. and 10 min later, was able to move the head almost completely to the left; pain on a visual analogue scale decreased from 5 to 1. Sedation was not modified.

These observations led us to think that propofol might be useful in the treatment of the acute phase of torticollis, and they show that propofol induces muscular relaxation, which seems to be efficient particularly when muscular spasm, contractions or rigidity are present [3]. Further studies to confirm these observations are welcomed.

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*British Journal of Anaesthesia* 1991; **66**: 531–533

# BOOK REVIEWS

*Handbook of Critical Care*, 3rd Edn. Edited by J. L. Berk and J. E. Sampliner. Published by Little, Brown and Company, Boston, Toronto, London. Pp. 812; indexed, illustrated. Price £32.50.

The editors of this "handbook" have brought together a distinguished team of experts to produce what they say is intended to be a practical guide on the care of critically ill patients. Unfortunately, at 800 pages, this can hardly be described as a handbook, and its practical advice is lost amongst many pages of close type.

This book represents a series of essays on different aspects of critical care medicine, rather loosely held together and slackly edited. It starts with a chapter on ethical issues—quite clearly a mistake, as an understanding of the ethical problems encountered in the Intensive Care Unit requires a prior knowledge of underlying medical problems. The following chapter on design of the Intensive Care Unit is unfortunately not relevant to United Kingdom practice, although some of its recommendations might usefully be followed by the D.H.S.S.

The sequence of the following chapters appears inappropriate. For example, the chapter on multiple organ failure is isolated from those on shock, ARDS and sepsis syndrome. It would also be more appropriate for the chapter on oxygen administration to precede that on ventilatory management.

Certain subjects are hidden from obvious view, for example the involvement of the gastrointestinal tract in multiple organ failure forms a substantial part of Chapter 4 on the general care of the critically ill patient, which is otherwise a rather superficial and inadequate review of overall patient care. Liver function in critical illness is considered only very briefly in the chapter on multiple organ failure.

Duplication is another major problem. For example oxygen transport, which is the supposed subject of Chapter 9, is repeated at length in Chapter 12, which covers the adult respiratory distress syndrome. Likewise, the classification of ventilators and ventilatory management, discussed in Chapter 10, is repeated at a basic level in Chapter 12. The problem of hypophosphataemia is mentioned briefly in various chapters throughout the book, but nowhere in depth.

Omissions are also a problem. The chapter on ARDS deals only with the pulmonary management. It does not address multiple organ failure aspects of the condition, although these are clearly most often the cause of death. Sedation of the patient undergoing ventilation barely rates a mention (12 lines: use of morphine sulphate, diazepam, and pancuronium in children). In the section on renal dysfunction, haemofiltration is not discussed—surely a major omission in an intensive care textbook. The concept of selective decontamination of the digestive tract is another topical subject which does not rate a mention.

Too often, when the reader might want an ordered treatment procedure, one finds a discursive essay, which will not help the reader in the acute situation and may indeed mislead him. This is seen in the descriptions of the management of acute renal failure, status epilepticus and increased intracranial pressure.

Tables and diagrams are rather few and, when present, are occasionally irrelevant. There is, for example, a table of synonyms for ARDS (25 in all) and another on the vegetable and animal products associated with hypersensitivity pneumonitis.

On a more positive note, there are several excellent chapters, such as those on haemodynamic and respiratory monitoring, acid–base disturbances and nutritional management. The book is mostly well referenced and in addition most chapters, but not all, have useful selected reading lists.

This book has a place, between the brief didactic texts and the major comprehensive textbooks of intensive care. It contains much useful information, but fails to realize its stated objective, that is to be a practical guide to the care of the critically ill.

*I. S. Grant*

*Clinical Anaesthesiology. Automated Anaesthetic Records*, 1st Edn. Edited by G. N. C. Kenny. Published by Baillière Tindall, London. Pp. 248; indexed; illustrated. Price £22.50.

The 21 chapters which comprise this book are written by 32 authors, from the United Kingdom, continental Europe and North America, representing many of the current investigators in this topic. They do their job well; that is, if their brief was to provide a review of their own interest in the subject and to summarize those of everyone else. There are, in other words, many repetitions and rehearsals of all the functions of any anaesthetic record and the virtues of any automated system.

It is not a book for the uninterested idle reader: it is full of jargon and abbreviations; the result for your reviewer was repeated attacks of somnolence.

"An anaesthetic record used for medico–legal purposes must be accurate, legible and complete", writes one author. Would that that were true! The truth is the exact opposite. The more inexact, illegible and incomplete, the greater is the use of the record by lawyers for the plaintiff. The lawyer for the defendant, in contrast, welcomes a perfect record. The failure of the concept of predictive risk to gain widespread acceptance is noted by another writer, but the given reason for this accurate observation omits the salient one: risk is derived normally from data about specific practices in specific locations and prediction may not be applicable to other practices in other locations. Each unit must have its own data and make its own predictions. Risk prediction has yet to be validated by comparative analyses from unit to unit.

Another statement: "that in the past, the quality of anaesthetic record keeping *was* poor" (my emphasis). The current variance in anaesthetic record keeping is unfortunately great, despite any (laudable) efforts by the College of Anaesthetists. The provision and use of anaesthetic records is one criterion for recognition of training posts. My experience in association with the National Confidential Enquiry into

Postoperative Deaths is that, whilst there are still institutions in the United Kingdom with anaesthetic records that leave much to be desired, there are others which have made improvements.

Most of the authors have developed their own computer system and each is naturally enthusiastic about their own. Not all extant systems are described; even from the United Kingdom there are some surprising omissions, so this book is not a comprehensive buyers' guide. One compact system (Lack) is very small and apparently inexpensive. The other two (Fisher, Naqvi) show all the signs of evolution into expensive, powerful and commercial packages. The European and American systems are already in this category and, although they have some appeal, they seem to be prohibitively expensive and complex. The latter disadvantage is recognized by everyone, although defensively it is noted that user resistance stems from unfamiliarity with the technique and this despite the 24-h presence of a systems supervisor! One automated system died before it was produced in quantity and one not entirely disinterested author revealed some of the inherent problems.

There are a few new thoughts in the last five chapters. These are overtly not so specific to individual systems and the writers consider alarms, the frequency of recording, philosophy of the presentation of data, economic aspects and medico-legal considerations, all in relation to automatic recording devices The last two chapters contain lucid arguments about the virtues of automated record keepers: they are *not* expensive in terms of all their potential and do not themselves pose a legal threat to those who use them.

There are several extremely unsatisfactory illustrations which purport to show detail which may be perceived only by the extremely faithful and trusting. One can understand readily how this happened, but surely a publisher could foresee the difficulties and encourage authors to produce more informative illustrations for their readers.

*J. N. Lunn*

*Introduction to Respiratory Care.* Edited by M. G. Levitzky, J. M. Cairo and S. M. Hall. Published (1990) by W. B. Saunders, Philadelphia. Pp. 589; indexed; illustrated.

This American text book is intended for "entry level students in certification programs and for those at the advanced practitioner level in registry programs in respiratory care". Respiratory therapy is a long-established paramedical specialty in North America with no exact parallel in the U.K. Thus the range of topics which are dealt with in this volume does not have an immediate appeal to a specific readership in the U.K. Nevertheless, the book does contain a wealth of clearly presented information which is of relevance to the clinical practice of physiotherapists, anaesthetists and chest physicians. The book is divided into three sections, the first on basic sciences, the second on clinical evaluation and the third on therapy. Of particular interest is the integration of cardiopulmonary function in a single volume. This is a distinct advance, as many text books focus on heart or lungs with little consideration of the important pathophysiological interactions of disease in one or both of these systems.

Each chapter has an outline at the beginning and contains a useful section on learning objectives. The chapters are very well illustrated with line diagrams, chest radiography and photographs of equipment, some diagrams being enhanced by a second colour to emphasize particular points. There is a very good index and a reasonably up-to-date reference section.

While probably not a volume for the personal library, this could well be near the top of the list for the departmental reference shelf.

*J. G. Jones*

*Clinical Neuroanesthesia.* Edited by R. F. Cucchiara and J. D. Michenfelder. Published by Churchill Livingstone, Edinburgh. Pp. 555; indexed; illustrated. Price £57.50.

This book is written by several authors, each with particular expertise relevant to neuroanaesthesia; all work, or have worked, at the Mayo Clinic. Although the content of the book is generally very good, the style of writing varies markedly, some chapters flow well, but others require substantial sections to be read again before the text can be fully understood. There is considerable repetition, particularly in physiology, pathophysiology and pharmacology of the cranial contents, which is wasteful of space and could have been edited out. In addition, there are several spelling mistakes which, in general, are obvious and do not detract from the understanding of the text. Each chapter provides a large number of references enabling the reader to follow up in detail any points of particular interest, and the inclusion of brief summaries of the potential complications of specific surgical and diagnostic procedures is a good feature of the book.

Chapter 1 provides a useful review of cerebral blood flow and metabolism. However, I would disagree with the statement on page 24 that, apart from a recent abstract, there are no reports of ICP increases after administration of opioids, and would point out that myoclonus caused by etomidate may increase ICP (p. 26). Chapter 2 gives an excellent review of cerebrospinal fluid dynamics and my only criticism is the use of cm $H_2O$ as units for ICP. Chapter 3 deals with intracranial pressure and factors which affect it. The argument on page 98 regarding the mechanism of the increase in CBF and ICP associated with coughing is not entirely convincing, because it does not take into account work which suggests that part of this increase in ICP is caused by an increase in vertebral venous blood volume secondary to an increase in CVP.

Chapter 4 describes electrophysiological monitoring in terms which make it interesting and easily comprehensible for anaesthetists. There are contradictory statements on page 147, but this chapter is generally well written and well illustrated. Chapter 5 is an excellent and very detailed review of cerebral protection. Unfortunately, the style of writing sometimes makes understanding difficult. The wording in the second paragraph on page 193 gives the mistaken impression that free radical scavenging causes irreversible cell damage and that hypothermia increases the effect of time on cell processes.

The anaesthetic management of surgery for cerebral aneurysm and arteriovenous malformation is described very thoroughly in chapter 6, but the style of writing sometimes makes understanding difficult, necessitating a second reading of some sections. On page 239 the author appears to imply that it is acceptable to close the dura whilst the patient is still hypotensive. Most neurosurgeons and neuroanaesthetists would not support such a practice.

Chapter 7 provides a very informative account of the anaesthetic implications of ischaemic cerebral vascular disease, but both this chapter and the next show examples of the repetition mentioned above. Chapter 8 describes the anaesthetic management of intracranial tumour surgery. The authors suggest that inhalation induction is acceptable in patients with cerebral tumours, when it is generally considered to be contraindicated in such patients. At the bottom of page 245, they refer to the performance of infratentorial craniectomy in the supine position which conjures up an interesting picture of the surgeons' posture! The authors also state that anaesthetic depth can be measured using mass spectrometry when it is anaesthetic agent concentration which is being measured.

Chapter 9 provides an excellent review of the classification of epilepsies and useful tables of therapeutic concentrations of anticonvulsants and potential toxicity. These probably reflect the contribution of the neurologist. Chapter 10 provides an interesting and very complete account of vertebral column and spinal cord surgery. My only criticism is the failure to mention compression of the carotid artery as a cause of cardiovascular instability during anterior cervical discectomy. Neuromuscular disorders and blocking agents are discussed in chapter 11, which is generally well written and has a long list of relevant references.

Stereotactic surgery is discussed in chapter 12. I found the detailed description of the surgical procedure very interesting, but a précis of this information would have been more useful for the trainee. The doses of lignocaine recommended for awake fibreoptic laryngoscopy and intubation appear large, with the potential for toxic reactions. Hydralazine is mistakenly described as an alpha- or beta-blocker.

The anaesthetic implications of neurodiagnostic procedures are very interestingly and concisely discussed in chapter 13. The brief summaries of the potential complications of specific procedures and the section on treatment of anaphylactoid reactions to contrast media are particularly useful. The chapter on neurointensive care is not very clearly written, and does not have a separate section on the intensive care management of head injury. I would question certain suggested management policies, including the use of sodium nitroprusside as first choice for controlling arterial pressure in ruptured intracranial aneurysm and the prophylactic use of glucose 25 g in status epilepticus, because there is a danger of incomplete cerebral ischaemia in this condition. However, there is a good section on postoperative management.

I was surprised to find a chapter on acute and chronic pain in a textbook on clinical neuroanaesthesia, but it gives a good review of the management of acute pain. The chapter on comas and brain death is excellent and gives useful lists of the different recommendations appearing in the world literature

In general, I found this a useful book which covered the subject of clinical neuroanaesthesia more than adequately Despite its few deficiencies, I enjoyed reading the book and learned much from it. Its style and content are not appropriate for trainees studying for the Part 3 F.C.Anaes. examination. This book is more appropriate for established neuroanaesthetists, who will probably wish to have a personal copy. It provides a good source of reference and senior registrars doing their neuroanaesthetic attachments would benefit from reading it. It would be a useful addition to anaesthetic department libraries and in my opinion it represents good value for money.

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"*I would have everie man write what he knowes and no more.*"—MONTAIGNE

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# EDITORIAL I

## MUSCLE ACTIVITY, pH AND MALIGNANT HYPERTHERMIA

Muscular work leads to an increase in both aerobic and anaerobic metabolism; the contribution of each is a function of the work rate and fitness of the individual. When muscle power output (i.e. the rate of ATP demand) exceeds the rate at which oxidative metabolism can generate ATP per muscle contraction, ATP is provided by intracellular creatine phosphate and anaerobic glycolysis. Lactate produced by anaerobic glycolysis accumulates in venous blood when the exercise intensity is sufficient to demand about 60% of the total body maximum oxygen consumption in sedentary people, or about 75% in endurance trained athletes [1]. Typically, maximum oxygen consumption is 45–55 ml $\text{min}^{-1}$ $\text{kg}^{-1}$ (about 15 times greater than resting values) in sedentary people and as great as about 70 ml $\text{min}^{-1}$ $\text{kg}^{-1}$ in endurance trained athletes. During high intensity work, when total body oxygen consumption is maximal, plasma lactate concentrations of approximately 12.0 mmol $\text{litre}^{-1}$ may frequently occur, although values as great as 30.0 mmol $\text{litre}^{-1}$ have been recorded [2]. This lactacidosis is associated with an accumulation of protons and a reciprocal decrease in plasma bicarbonate concentrations. Blood pH decreases from 7.4 to as little as 6.8, while i.m. pH decreases from 7.0 to as little as 6.4 after exhaustive dynamic exercise of less than 6 min duration [3, 4].

Similar acid–base disturbances occur during sustained isometric muscle contraction [5]. If isometric muscle contraction is sustained for at least 45 s at greater than 25% of the maximum voluntary force of contraction, compression of the muscle vasculature by the contracting muscle fibres causes ischaemia. The reduced supply of oxygen to the mitochondria makes anaerobic glycolysis necessary to generate ATP for muscle contraction.

Thus there are two distinctly different reasons for a decrease in muscle pH during muscular work. It may be caused either by the increased rate of ATP demand that occurs during vigorous dynamic exercise, or by the reduced oxygen supply that occurs during sustained isometric muscle contraction.

Usually, muscle activity is reduced under anaesthesia because of both induced muscle quiesence, consequent upon CNS depression, and the direct effects of drugs acting on muscle (including neuromuscular blockers) and membrane stabilizing agents such as local anaesthetics. Under these conditions, muscle blood flow decreases to around 50 ml $\text{min}^{-1}$ $\text{kg}^{-1}$ as a result of the reduced oxygen consumption and reduced activity-related metabolism.

However, under some circumstances, muscle activity may be greatly increased. Shivering in the period immediately after operation may be so violent as to increase total body oxygen consumption to 5 times resting value. Status epilepticus can cause such an increase in total body metabolism as to produce life threatening hyperthermia and hypoxia. Muscle spasm, caused for example by the action of suxamethonium, while not increasing metabolism to more than twice normal, is a potent cause of lactacidosis, as a result of the effect of the contracted muscle on muscle blood flow. Eventual relaxation of the contracted muscles allows the release of the accumulated lactic acid and a rapid decrease in blood pH.

An altogether more sinister type of muscle spasm is that associated with malignant hyperthermia (MH). In this state, the concomitant muscle contracture with the associated reduced muscle blood flow, and metabolism increased (perhaps independently) to around five times basal, results in severely reduced muscle and eventual blood pH; this often decreases to less than 7.0.

Malignant hyperthermia is seen also in several breeds of swine and, indeed, most of what we know of the acute MH episode has been gleaned from experimental work on pigs. However, in addition to anaesthetic agents, many forms of "stress" such as exercise, hot environments, crowding, transport, copulation etc., trigger porcine MH. Several years ago Wingard [6] expressed the view that MHS humans were also liable to develop the syndrome when stressed, and he produced several accounts of unexplained fever and unexpected death in members of known MHS families. He proposed that MHS individuals were liable to develop the acute syndrome when exposed to hot environments, trauma, severe excercise etc., and so should avoid exposing themselves to such factors for fear of "awake triggering". However, satisfactory documentation of such episodes is scant [7] and no such occurrences are known to the Leeds MH Investigation Unit.

In order to determine whether or not MHS patients react to "stress" differently from normal individuals, the Leeds group in the late '70s and early '80s conducted several studies at mild exercise [8], progressively severe exercise [9], steady state exercise [10] and cold exposure [11] in MH-susceptible volunteers. Differences were found: these were small and were only apparent on measurement and not obvious to the subjects but, with the exception of mild steady state exercise [10], they were consistent with increased activity in the sympathetic nervous system. Stanec and Stefano [12] have independently demonstrated greater circulating concentrations of cyclic AMP in MHS subjects following a brief period of progressively severe exercise, although their study design was criticized as it made no allowances for individual levels of physical fitness [13].

The sympathetic nervous system is involved in porcine MH, but it is debatable if this is a primary or secondary phenomenon. The most obvious site for some abnormality would be skeletal muscle [14]. Ellis and colleagues [15] have shown abnormalities in MHS skeletal muscle removed at biopsy, with small glycogen and greater lactate concentrations, possibly as a result of greater rates of glycolysis, although Hall and Lucke [16] using a cryoprobe biopsy technique in pigs could demonstrate no abnormalities in MH susceptible animals. More recently, Rutberg and colleagues [17] exercised MHS volunteers for two periods of 15 min at 40% and 80% of their maximal oxygen uptake, and measured several metabolites and hormones, including catecholamines. They also were unable to demonstrate any consistent differences between the MHS and control groups.

Further objective indirect evidence can be obtained by the type of study reported in this issue by Allsop and colleagues [18], who demonstrated a difference between MHS muscle recovery after short-duration violent exercise compared with controls. The attraction of this study is the use of direct measurement of muscle pH as opposed to indirect inference of muscle pH from nuclear magnetic resonance spectroscopy (a technique which has the one major advantage of being non-invasive). The Allsop study relied on the use of an *in vivo* pH muscle probe which was reinserted immediately after muscular exertion had terminated.

Another strength of this study is their use of patients who were unequivocally MHS using the *in vitro* halothane and *in vitro* caffeine challenge tests as agreed by the European MH Group. If MH status is unconfirmed, or even if non-standard tests which have not been validated with appropriate controls are used, the results must be viewed with suspicion. Such a study was reported by Laschuk and colleagues [19], who assumed "K-type" patients to be MH susceptible—yet it is accepted that the K-type *in vitro* caffeine reaction occurs in about 10% of the general population, and is unlikely, therefore, to be associated with MH, which is a clinically rare condition.

Phosphorus-31 NMR spectroscopy has been performed by Olgin and colleagues [20] in subjects who have been demonstrated convincingly to be MHS. Using a forearm exercise test, they showed the MHS individuals had delayed recovery of muscle phosphocreatine, inorganic phosphate and ATP to pre-exercise values. They found no significant difference between the two groups in the relationship of work rate to the inorganic phosphate:phosphocreatine ratio. Kozak-Reiss, Gascard and Redouane-Benichou [21] also found delayed recovery of muscle metabolites and indirectly measured pH in both MHS subjects and elite athletes in forearm muscles after excercise. Their MHS subjects were screened as in the Allsop study, using the European MH screening procedure.

If MHS muscle tissue differs significantly from normal in response to exercise, there are two potentially important outcomes. First, NMR screening could be used to detect MH susceptibility in a non-invasive way, although it is likely that more specific DNA screening may be developed first. Second, it demonstrates that there is a "physiological" abnormality in the muscle which is consistent with the envisaged defect in the ryanodine calcium receptor in the sarcoplasmic reticulum, which has been proposed recently to be the most likely site for the MH muscle defect [22].

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*J. H. Green and*
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# EDITORIAL II

## TRAINING IN FIBREOPTIC LARYNGOSCOPY

The past decade has seen rapid advances in fibreoptic technology. Increasingly, these advances are being used in medicine, particularly gynaecology, urology, gastroenterology and chest medicine. Currently, the main uses in anaesthesia are to accomplish and confirm difficult tracheal intubation, and inspection of the lower respiratory tract before endobronchial intubation. Uses in the intensive care unit are increasing, while other indications are beginning to emerge [1], for example using fibreoptic instruments to pass nasogastric tubes under difficult circumstances.

Unusually, the specialty of Anaesthesia has been somewhat slow in taking advantage of these new developments. The main reason for such delay has probably been the cost of each specialized piece of equipment. In the U.K., the current financial situation may have restricted large departments to possession of only one, while smaller departments frequently do not possess such an instrument. However, at this stage of development of anaesthesia, it is important that all departments should acquire a fibreoptic laryngoscope. Instrument care and training programmes must be introduced. It is essential that each anaesthetist is taught how to look after the instrument correctly to prevent unnecessary damage. It is also essential that the instrument is cleaned correctly; particular care should be taken to clear and test the suction biopsy channel, otherwise the instrument may be ruined. The sterilization programme should be taught well, although some excellent commercial systems are readily available.

Training in the use of fibreoptic laryngoscopy is more difficult [2, 3]. There may be a suitably trained person in a department who may assume the role of instructor. If not, a consultant member of the department should visit other centres where a programme exists, to acquire personal experience.

Aids have been devised in positioning of the fibreoptic laryngoscope to view the larynx. One of the most popular in the United Kingdom is the Berman Mark II split airway [4]; when it is inserted into the mouth in the mid-line, its distal end is sited in the region of the rima glottidis. In some other parts of the world, the Patel Syracuse [5] mask is popular. Inevitably, the laryngeal mask airway (LMA) has been utilized also to enable trainees to see the vocal cords [6]. The use of commercial dummies has also been shown to be useful. Indeed, when comparing the use of simulators with traditional teaching methods, Ovassapian [7] concluded that the former method was associated with subsequent greater success rates in patients.

Theoretically, each trainee should practise fibreoptic tracheal intubation of subjects who are under sedation and local anaesthesia. Some may consider this unethical and, therefore, it may be necessary for practice to be undertaken in subjects under general anaesthesia. However, some anaesthetists have used this technique not only when there are clinical indications, but also in daily practice and teaching. During training, it would be advisable to restrict practice to conventionally prepared ASA I or II grades of patients.

Is it justifiable to use a fibreoptic instrument for tracheal intubation in the absence of specific indications? To answer this question requires consideration of the physiological changes induced by fibreoptic laryngoscopes. Equally controversial is the route used. Should the trainee use the nasal or oral route for intubation? The evidence suggests that the nasal approach may initially be more successful [7]. However, there is a body of opinion which states that the route chosen should be appropriate to the type of surgery undertaken—for example a nasal route for facio–maxillary surgery.

Whichever routes or aids are used, the key to success in fibreoptic tracheal intubation is to identify set distances and anatomical structures before advancing the instrument. An example would be to measure the distance between the angle of the mouth and the tragus of the ear; this is approximately equal to the distance from the lips to the rima glottidis. The fibrescope is passed through the mouth in the midline into the pharynx to that distance, while the jaw is pulled forward to open up the pharyngeal space. If the cords are not seen, the instrument should be moved forwards 2 cm. With patience, the vocal cords may be seen, the fibrescope passed through and the carina identified. The tracheal tube is "rail roaded" over the scope into the trachea, although this may occasionally be difficult and the recommendations of Dogra, Falconer and Latto [8] may be helpful with this manoeuvre. If the carina is seen, and the end of the tracheal tube seen on withdrawal of the instrument, one may assume successful intubation. Despite this visual confirmation, stethoscopy and auscultation are mandatory.

It is during this period that the main problems may arise. It has been shown that the use of a fibreoptic method for tracheal intubation takes at least three times longer than conventional methods [9]. There is therefore the possibility that hypoxaemia, hypercapnia and awareness can occur. It would seem prudent both to preoxygenate the patient's lungs fully and to monitor the patient using a pulse oximeter before embarking on fibreoptic intubation. It is essential also that a trained anaesthetic nurse or an operating department assistant is present to observe both the ECG and oxygen saturation.

It is important to guard against awareness. If an inhalation technique is well established, it is unlikely that the increased time needed to achieve intubation may lead to awareness. However, in the presence of an i.v. induction which also utilizes a neuromuscular blocking drug, there may be a chance of patient awareness developing. It may be appropriate, therefore, to hyperventilate the lungs after induction with high concentrations of oxygen and a volatile agent immediately before embarking on the procedure. Research is required to define the optimum agents for both premedication and induction under these circumstances.

Although the cardiovascular responses to fibreoptic intubation are similar to those caused by conventional methods, these changes are more prolonged [9], and this may preclude its use in some patients. However, it has been shown that if a "steady state" of anaesthesia has been achieved, these responses are obtunded [10].

Another potential problem associated with prolonged intubation time is an increased risk of gastric regurgitation and aspiration into the respiratory tract. However, Ovassapian and colleagues did not find this a major problem, despite the fact that all patients in their study underwent tracheal intubation under sedation and local anaesthesia [11]. It is thought that, although the upper respiratory tract is anaesthetized, lower respiratory tract reflexes remain intact; as the patient is awake, any inhaled foreign material promotes coughing and subsequent rejection. This is clearly a controversial area. Interestingly, there is no difference in the incidence of sore throat compared with conventional methods of tracheal intubation.

It seems, therefore, that there are both advantages and disadvantages associated with fibreoptic tracheal intubation. However, if it is considered mandatory under some circumstances, it must be essential that anaesthetists become competent in the use of fibreoptic instruments and that training is provided.

Occasionally, during rigid bronchoscopy, it may be impossible to inspect thoroughly some anatomical structures, for example, the right upper lobe bronchus. Under these circumstances, a fibreoptic bronchoscope may be passed through a rigid instrument and an inspection made which will provide information on possible surgical therapy. The use of a Storz rigid fibreoptic bronchoscope also allows excellent visual appreciation and, at the same time, enables the anaesthetist both to provide oxygenation and to anaesthetize the patient.

Endobronchial intubation also may be accomplished with fibreoptic instruments, particularly when single lumen tubes are used. Currently, it is extremely difficult to obtain the Magill and Mansfield intubating bronchoscopes [12], and it is fortuitous that fibreoptics have enabled rigid and flexible instruments to take their place [13, 14].

The uses of fibreoptic instruments in the intensive care unit (ICU) are increasing [15]. There are many reasons for obtaining chest radiographs in ICU patients; one is to confirm the position of the tip of the tracheal tube. If there is no other reason to request a chest x-ray, inspection with a fibreoptic bronchoscope may confirm the position of the tracheal tube. The suction port may be used also to remove secretions although, it must be admitted, not very effectively when these are tenacious. As the risk of cross infection in an ICU is already a major cause of anxiety, factors which may increase that risk must be evaluated critically. This reinforces the need for appropriate training in fibrescope care and correct sterilization between cases.

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# DELAYED RECOVERY OF MUSCLE pH AFTER SHORT DURATION, HIGH INTENSITY EXERCISE IN MALIGNANT HYPERTHERMIA SUSCEPTIBLE SUBJECTS

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AND G. M. HALL

## SUMMARY

*Six subjects susceptible to malignant hyperthermia (MHS) and seven control subjects exercised for 4 min at 120% of their calculated maximal oxygen uptake on a bicycle ergometer. Mean (SEM) muscle pH, measured with a needle-tipped electrode in the vastus lateralis muscle, decreased from a resting value of 7.16 (0.04) to 6.78 (0.04) after exercise in the control group, and from 7.15 (0.05) to 6.56 (0.05) in the MHS group ($P < 0.01$ compared with control group). A further decrease in muscle pH to 6.68 (0.06) by 5 min after exercise occurred in the control group, followed by incomplete recovery to 7.06 (0.04) 30 min after exercise. In the MHS group, however, muscle pH decreased to 6.45 (0.05) 5 min after exercise before recovering slowly to only 6.64 (0.07) after 30 min ($P < 0.01$ compared with control group). There was no difference in muscle temperature, venous pH or venous lactate concentrations between the two groups. The results show that there is abnormal recovery of muscle pH after short-duration, high-intensity exercise in MHS subjects.*

**KEY WORDS**

*Hyperthermia: exercise test, malignant Metabolism: lactate, muscle pH.*

Malignant hyperthermia is a rare condition in which susceptible individuals (MHS) develop a hypermetabolic response of skeletal muscle after challenge by certain triggering agents [1]. Although volatile anaesthetic agents and depolarizing neuromuscular blocking drugs are the most commonly implicated triggering agents in man, stress and severe exercise have also been proposed [2, 3]. There are conflicting reports of the effects of exercise in MHS subjects. Campbell and colleagues [4] and Stanec and Stefano [5] reported that there was increased sympathetic activity during exercise in MHS subjects, but this was not found by Rutberg and co-workers [6], who also failed to find any difference in muscle metabolites between MHS and normal subjects after exercise.

There is evidence from phosphorus-31 nuclear magnetic resonance spectroscopy ($^{31}$P-NMR), however, of decreased muscle pH immediately after high-intensity arm exercise in MHS subjects [7]. Another NMR study showed a decreased rate of recovery of the inorganic phosphate: phosphocreatine ratio after arm exercise in MHS individuals, suggesting continuing ATPase activity [8]. The purpose of the present study was to compare the recovery profiles of muscle pH and temperature in MHS and control subjects after high-intensity, short-duration exercise on a bicycle ergometer.

## SUBJECTS AND METHODS

The study, performed in Linkoping, was approved by the local Ethics Committee and all subjects gave consent after a full explanation of the procedures and possible risks involved. We

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*This article is accompanied by Editorial I.*

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TABLE I. *Subject characteristics and power output data (mean (SEM)). * $P < 0.05$ between groups*

| | Control ($n = 7$) | | MHS ($n = 6$) |
|---|---|---|---|
| Sex (M/F) | 6/1 | | 6/0 |
| Age (yr) | 36 (1) | | 33 (5) |
| Height (m) | 1.83 (0.02) | | 1.78 (0.03) |
| Weight (kg) | 75.6 (3.6) | | 77.2 (4.5) |
| Mean power (W) | 327 (20) | | 290 (18) |
| Power/weight (W $kg^{-1}$) | 4.3 (0.1) | * | 3.8 (0.2) |

studied six MHS subjects who had been diagnosed by *in vitro* testing of muscle biopsies at the University of Lund according to the criteria of the European MH Group [9]. The control group comprised seven subjects recruited from the hospital staff. Characteristics of all subjects are shown in table I. The maximal oxygen uptake ($Vo_2$max) of each subject was calculated from a submaximal cycle test conducted on a previous occasion according to the method of Astrand and Ryhming [10]. All subjects undertook exercise only for recreational purposes and had similar levels of habitual activity.

After an overnight fast, each subject had an area of skin over the mid-part of the vastus lateralis muscle cleaned with alcohol and infiltrated with 2% lignocaine. The needle-tipped pH electrode (20-gauge, World Precision Instruments) and the NiCr/NiAl thermocouple (21-gauge, Comark) were inserted into the muscle 1 cm apart and resting values measured. Blood samples were collected from a cannula in a forearm vein for measurement of baseline pH, $Po_2$, $Pco_2$ and lactate concentrations. The ECG of each subject was displayed continuously throughout the study.

The pH electrode and thermocouple were removed and all subjects undertook the following exercise test: a 1-min warm up was undertaken at a work load equivalent to 60% $Vo_2$max, then after a 1-min rest, a further 4 min of exercise was performed at a work load equivalent to 120% $Vo_2$max. Most subjects needed considerable encouragement to complete this stage of the procedure. The exercise test was conducted with the subject in an upright posture on an electrically braked and compensated bicycle ergometer. On completion of the exercise, the subject was transferred rapidly to a couch and the pH and temperature probes reinserted into a second, pre-prepared site in the same muscle, at least 5 cm from the initial insertion. During the 30-min recovery period, muscle pH and temperature were measured continuously and blood samples were collected. The pH and temperature probes remained undisturbed during the recovery period.

The pH electrode was connected to a Corning M140 pH meter and, between subjects, was cleaned with acetone, sterilized in glutaraldehyde and washed liberally in sterile water. The electrode was calibrated before and after each insertion against standard pH buffers of 4.00, 7.00 and 10.00 (20 °C). The pH values obtained in the study were not corrected for temperature. The precautions necessary to ensure rapid response of the pH electrode (3 s) with good stability over a prolonged period of time were described in detail by Allsop and colleagues [11]. The thermocouple was linked to a Comark 2001 meter and the system calibrated against a mercury-in-glass reference thermometer. The thermocouple was cleaned and sterilized in the same manner as the pH electrode. Venous lactate concentrations were determined by standard enzymatic methods [12].

Results are presented as mean values (SEM). Data were analysed by two-way and one-way analysis of variance as appropriate.

## RESULTS

There was no significant difference between subject characteristics and power output of the MHS and control subjects except for a significantly decreased ($P < 0.05$) power to weight ratio in the MHS group (table I).

Muscle pH decreased significantly ($P < 0.01$) in response to exercise in both groups: from 7.16 (0.04) to 6.78 (0.04) in the control group, and from 7.15 (0.05) to 6.56 (0.05) in the MHS group (fig. 1). Muscle pH continued to decrease during the early part of the recovery period to a nadir of 6.68 (0.06) in the control group and 6.45 (0.05) in the MHS group after 5 min. Thereafter, pH recovered progressively in the control group to 7.06 (0.04) after 30 min, whereas recovery was delayed in the MHS group and muscle pH attained only 6.64 (0.07) after 30 min. Throughout the recovery period, the muscle pH in the MHS group was significantly less than the control group ($P < 0.01$ from 0 to 10 min recovery and $P < 0.001$ from 10 to 30 min recovery).

Muscle temperature increased similarly in both groups, from 36.1 (0.3) °C to 38.1 (0.1) °C ($P < 0.001$) after exercise in the control group and from 36.2 (0.2) °C to 38.3 (0.2) °C ($P < 0.001$) in the

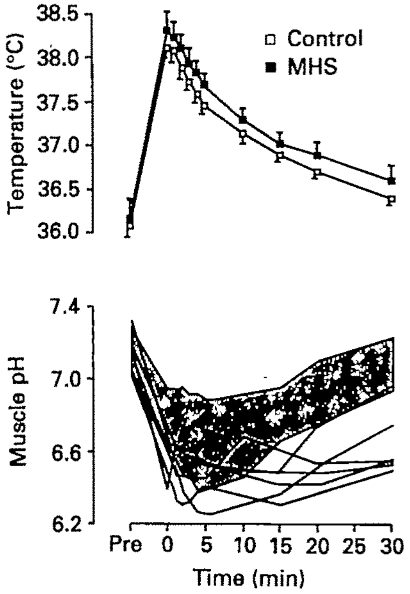

FIG. 1. Mean (SEM) muscle temperature and pH changes at rest (Pre) and after exercise. pH changes are shown as a shaded area which represents the range of values measured in the control group, and as lines which represent individual MHS subjects.

MHS group (fig. 1). Recovery of muscle temperature occurred rapidly after completion of exercise and values had decreased to 36.4 (0.1) °C in the control group and 36.6 (0.2) °C in the MHS group after 30 min. There was no significant difference in muscle temperature between the two groups throughout the study.

There was no significant difference in venous lactate concentrations, venous pH, venous $P\text{O}_2$ and venous $P\text{CO}_2$ between the two groups (table II). Peak heart rate values occurred during the 4th minute of exercise (179 (5) beat $\text{min}^{-1}$ in the control group and 186 (4) beat $\text{min}^{-1}$ in the MHS group) and were still increased after 30 min recovery (table II). There was no significant difference in the heart rate response to exercise between the two groups.

## DISCUSSION

The principal finding of this study is that muscle pH showed both a greater decrease and a delayed recovery after high-intensity, short-duration exercise in MHS subjects. This persistent acidosis of exercised muscle occurred in the presence of similar increases in muscle temperature and comparable changes in venous pH and circulating lactate concentrations.

We have previously used the needle-tipped pH electrode to measure sequential changes after a 30-s sprint in man [11]. The relationship between muscle pH obtained with the pH electrode and with other methods of measurement has not yet been determined. The homogenate technique has been used for nearly 20 years to ascertain the pH of muscle biopsies [13]. Measurement of pH by this technique commonly gives values of about 7.0 [14], which is less than the 7.1–7.2 observed in this study. However, the absolute decrease in pH of 0.5–0.6 in response to maximal exercise in normal subjects is similar with both techniques [11]. The homogenate method of pH determination gives values which represent both intra- and extracellular compartments. We have suggested that the slightly greater resting pH values observed with the pH electrode reflect a greater contribution from the extracellular space

TABLE II. *Mean (SEM) venous pH, $P\text{O}_2$, $P\text{CO}_2$, lactate and heart rate before (Pre) and after exercise in control and MHS subjects*

| Time (min) | pH | | $P\text{O}_2$ (kPa) | | $P\text{CO}_2$ (kPa) | | Blood lactate (mmol $\text{litre}^{-1}$) | | Heart rate (beat $\text{min}^{-1}$) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Control | MHS | Control | MHS | Control | MHS | Control | MHS | Control | MHS |
| Pre | 7.38 (0.01) | 7.38 (0.01) | 6.0 (0.3) | 6.0 (0.4) | 6.1 (0.4) | 6.2 (0.2) | 0.9 (0.1) | 0.7 (0.1) | 75 (4) | 77 (5) |
| 0 | 7.01 (0.06) | 7.08 (0.02) | 5.8 (0.9) | 4.9 (0.5) | 10.0 (0.9) | 9.8 (0.3) | 15.8 (2.2) | 12.2 (1.3) | 169 (1) | 174 (5) |
| 1 | 7.03 (0.05) | 7.12 (0.02) | 8.0 (1.1) | 6.0 (0.8) | 9.6 (1.1) | 7.7 (0.3) | 14.7 (1.0) | 11.9 (1.5) | 147 (3) | 149 (8) |
| 2 | 7.09 (0.03) | 7.14 (0.02) | 8.9 (0.6) | 7.1 (0.8) | 6.2 (0.8) | 6.5 (0.4) | 14.4 (1.4) | 12.9 (1.4) | 129 (5) | 136 (8) |
| 3 | 7.10 (0.04) | 7.14 (0.02) | 9.2 (0.7) | 7.8 (0.8) | 5.8 (0.5) | 5.9 (0.5) | 15.5 (0.9) | 13.5 (1.4) | 119 (3) | 126 (6) |
| 4 | 7.08 (0.03) | 7.13 (0.03) | 9.8 (1.0) | 8.3 (0.9) | 5.3 (0.4) | 5.5 (0.5) | 16.3 (1.1) | 13.8 (1.3) | 118 (4) | 124 (6) |
| 5 | 7.09 (0.03) | 7.13 (0.02) | 10.1 (1.1) | 8.7 (1.1) | 5.1 (0.4) | 5.4 (0.4) | 16.0 (0.9) | 14.4 (1.3) | 112 (3) | 121 (6) |
| 10 | 7.11 (0.03) | 7.13 (0.02) | 9.0 (1.0) | 8.7 (0.7) | 4.9 (0.2) | 5.1 (0.4) | 15.2 (0.9) | 14.0 (1.3) | 109 (3) | 116 (4) |
| 15 | 7.15 (0.03) | 7.16 (0.02) | 8.6 (1.1) | 8.6 (0.8) | 4.7 (0.2) | 4.8 (0.3) | 13.9 (0.9) | 13.6 (1.2) | 106 (3) | 113 (5) |
| 20 | 7.19 (0.03) | 7.18 (0.02) | 8.4 (0.8) | 8.3 (0.7) | 4.6 (0.2) | 4.7 (0.3) | 12.3 (1.1) | 12.9 (1.4) | 104 (2) | 111 (4) |
| 30 | 7.28 (0.02) | 7.25 (0.02) | 7.0 (0.5) | 7.5 (0.6) | 4.7 (0.2) | 4.6 (0.2) | 9.1 (1.0) | 10.6 (1.2) | 102 (4) | 108 (4) |

with this technique [11]. $^{31}$P-NMR determines the intracellular pH of muscle indirectly and yields resting values for forearm muscle of 7.0–7.1 [15, 16]. The decrease observed with exercise is slightly greater than that found with the biopsy technique with values as small as 6.24 observed [16].

Laschuk and colleagues also reported a delayed recovery in forearm muscle pH after exercise, as measured by $^{31}$P-NMR [7]. Their data showed no difference in resting pH between control and MHS subjects (7.06 and 7.03, respectively) or on mild exercise. It was only in the recovery phase after severe exercise that a difference was observed (6.64 in control subjects and 6.40 in MHS subjects). Our results agree with these initial observations of Laschuk's group [7]. Olgin and colleagues [8] also used $^{31}$P-NMR to study changes in high-energy phosphate compounds during forearm exercise in MHS subjects. They stated that there was no difference in muscle pH between control and MHS subjects at rest or during exercise, but no values were cited for the recovery period. Furthermore, as the total exercise period was 18 min, it is unlikely that the severity of the exercise was sufficient to produce the profound acidosis found in the present study.

The delayed recovery in muscle pH after severe exercise in MHS subjects indicates either continuing production or delayed removal of lactic acid from muscle, or both. Lactic acid production is considered currently to reflect changes in the redox state of the muscle and not simply an oxygen deficient state [17]. In MHS subjects, abnormally increased intracellular [$Ca^{2+}$] during recovery from exercise would result in continuing activation of the myofibrillar ATPase with increased ADP and inorganic phosphate concentrations within muscle. These changes stimulate glycolysis and increase the cytosolic NADH concentrations. This reduction in redox potential shifts the lactate dehydrogenase equilibrium towards increased lactate production. It is interesting that Olgin and colleagues [8] found a slower rate of recovery of the inorganic phosphate:phosphocreatine ratio after forearm exercise in MHS subjects—conditions that would favour increased lactate production.

Lactic acid disposal in muscle occurs by two main pathways. Some lactate is metabolized *in situ* [18], whilst the remainder is removed by a lactate transporter in the sarcolemma which shows saturation kinetics [19]. The rate-limiting nature of this important mechanism for removal of intracellular lactate may account for the dissociation observed in the present study between muscle pH, and circulating lactate and pH values. Increased intracellular concentrations of lactate after intense exercise cannot be in equilibrium with extracellular concentrations until sufficient lactate has been either metabolized or transported to ensure that the translocation mechanism is not saturated. Subsequent removal of lactate from the extracellular space depends on the local buffering and muscle perfusion. Some of these steps in lactate disposal may be abnormal in MHS subjects and contribute to the persistent acidosis of muscle.

Changes in muscle temperature in response to exercise were similar in both groups, although the mean power output was significantly less in MHS subjects. We cannot exclude the possibility that, at comparable work loads, the MHS group would have shown greater thermogenesis, but our recent work suggests that muscle temperature is not affected greatly by small changes in power output [Hall and Allsop, unpublished data]. The decreased power output in the MHS subjects may reflect the underlying myopathy which is manifest only during high-intensity exercise and is not apparent at normal levels of activity.

In conclusion, we have shown delayed recovery of muscle metabolism after exercise at 120% $\dot{V}o_2$max in MHS subjects. This is in contrast to our previous work in which no metabolic abnormalities were found in MHS subjects after exercise at 40% and 80% $\dot{V}o_2$max [6]. Further studies are required to confirm our results, together with direct measurement of changes in muscle lactate concentrations, by either sequential biopsies or proton NMR.

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# COMPARISON OF TWO METHODS OF FIBRESCOPE-GUIDED TRACHEAL INTUBATION

## J. E. SMITH, A. A. MACKENZIE AND V. C. E. SCOTT-KNIGHT

### SUMMARY

*We have compared intubation time and cardiovascular effects of fibrescope-guided orotracheal intubation aided by the Berman 11 Intubating Airway with those of the tongue traction method of fibreoptic intubation and with conventional Macintosh intubation. We studied 75 patients who received a standard general anaesthetic which included non-depolarizing neuromuscular block; they were allocated randomly to one of the three groups immediately before intubation. The mean time required to effect Berman airway intubation (34.9 s) was similar to that required for tongue traction intubation (35.3 s) and significantly greater than that required for Macintosh intubation (11.7 s). The cardiovascular responses to both types of fibreoptic intubation were significantly greater and more prolonged than those of Macintosh intubation. There were no significant differences between the responses to the two fibreoptic techniques. Haemodynamic effects should be considered when performing fibrescope-guided tracheal intubation under general anaesthesia and, when necessary, appropriate measures should be taken to minimize them.*

**KEY WORDS**

*Intubation, tracheal: technique, complications. Equipment: fibreoptic laryngoscope.*

The fibreoptic laryngoscope may permit tracheal intubation, often with ease, in awake or anaesthetized patients, when traditional methods have failed [1,2]. However, it has been shown that fibrescope-guided orotracheal intubation facilitated by anterior traction on the tongue under general anaesthesia requires a prolonged intubation time and produces greater pressor and heart rate changes than intubation with the Macintosh laryngoscope [3].

Several types of pharyngeal guide and airway have been developed to facilitate fibreoptic laryngoscopy [4–8]. One of these devices, the Berman 11 Intubating Airway [9,10], is inexpensive and appears suitable for use as an aid to fibreoptic intubation, although it was introduced originally as an aid to blind intubation. It comprises a divided oropharyngeal airway through which the fibrescope can be passed co-axially and delivered close to the vocal cords. When the tip of the laryngoscope has been advanced a short distance into the trachea, the airway, which has a plastic hinge down the left side and a lateral opening down the right side, can be prized open and released from around the body of the laryngoscope. The tracheal tube may then be guided into the trachea over the laryngoscope. Use of this airway obviates the need for extrusion of the tongue and may reduce the amount of fibrescope manipulation required and the degree of fibrescope contact with pharyngeal mucosa. A decrease in pharyngeal stimulation might result in a decrease in reflex sympathetic activity and, if the airway enables fibreoptic intubation to be performed more rapidly, this may also minimize cardiovascular changes, since Stoelting has shown that increasing the duration of laryngoscopy increases the pressor response [11].

The object of this study was to compare the intubation time and cardiovascular responses of fibreoptic intubation aided by the Berman airway with those of fibreoptic intubation facilitated by

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*This article is accompanied by Editorial II.*

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TABLE I. *Age, weight and sex characteristics (mean (SEM) where applicable)*

| | Age (yr) | Weight (kg) | Sex (M/F) |
|---|---|---|---|
| Control group (*n* = 25) | 33.0 (1.5) | 64.3 (2.4) | 4/21 |
| Tongue traction group (*n* = 25) | 32.4 (1.6) | 61.9 (2.3) | 6/19 |
| Berman airway group (*n* = 25) | 32.3 (1.6) | 65.0 (2.5) | 5/20 |

anterior tongue traction and with conventional intubation using the Macintosh laryngoscope.

## PATIENTS AND METHODS

The study was approved by the Ethics Committee of the South Birmingham Health Authority and informed written consent was obtained from each patient. We studied 75 ASA class I or II patients aged 16–50 yr, undergoing elective gynaecological or general surgery requiring orotracheal intubation and mechanical ventilation of the lungs. Patients taking vasoactive drugs, the morbidly obese, those with a history of acid reflux or hiatus hernia and those in whom difficult intubation was expected were excluded from the study.

Patients were premedicated 1 h before surgery with temazepam 20 mg orally. On arrival of the patient in the anaesthetic room, an appropriate vein was cannulated and the ECG monitored continuously. Arterial pressure and heart rate were measured at 1-min intervals using a recently calibrated Dinamap 1846 oscillotonometer and recorded with a Dinamap TR2000 printer. After a stabilization period of at least 5 min, baseline recordings were taken and anaesthesia was induced with a dose of thiopentone sufficient to obtund the eyelash reflex (usually 5 mg $kg^{-1}$), followed by vecuronium 0.125 mg $kg^{-1}$. The patient's lungs were ventilated with 1 % isoflurane and 50 % nitrous oxide in oxygen using a Bain system and face mask with an initial fresh gas flow of 90 ml $kg^{-1}$ $min^{-1}$. A Datex Normocap capnometer sampling catheter was placed under the face mask and fresh gas flow rate and ventilation were adjusted to maintain the end-expired carbon dioxide concentration at 4.5–5 %. After 2 min of ventilation of the lungs, the patients were assigned on a random number basis (using sealed numbered envelopes) to the control group (intubation with the Macintosh laryngoscope), the tongue traction group (intubation with an Olympus LF-1 fibreoptic laryngoscope with the aid of controlled tongue traction applied by an assistant) or to the Berman airway group (fibreoptic intubation using a Berman intubating airway). A Berman airway was then inserted into the pharynx in those patients assigned to the Berman group (medium size (90 mm) for males and small size (80 mm) for females) and a Guedel airway (size three for males and size two for females) was inserted into the pharynx of patients assigned to the other two groups. After a further 2-min period of ventilation, tracheal intubation was performed.

The tongue traction fibreoptic intubations were carried out as described previously [2,3]. In the Berman fibreoptic intubations, the chin was elevated and the atlanto-occipital joint hyperextended by an assistant. The fibreoptic laryngoscope (onto which a tracheal tube had previously been threaded) was advanced through the airway, manipulated between the vocal cords, and advanced approximately 7.5 cm into the trachea. The Berman airway was then disengaged from the fibrescope, by means of the lateral opening, and withdrawn from the pharynx, and the tube was guided into the trachea by the fibrescope. Disposable, cuffed, Portex tracheal tubes (size 9 mm for males and size 8 mm for females), lubricated with KY jelly, catheter mount attached were used in all subjects. Successful intubation was confirmed by capnography. The intubation time was taken as the interval between removal of the face mask from the patient's face and reconnection of the Bain system to the catheter mount after intubation had been completed. If any intubation could not be completed within 60 s, the patient was withdrawn from the trial and the cardiovascular data obtained were not included in the results. Arterial pressure and heart rate measurements were continued for 5 min following successful tracheal intubation, after which surgery was allowed to proceed.

TABLE II. *Time to achieve successful intubation (mean* (SEM) *[range]).* *$P < 0.05$ *compared with control values*

| Group | Time (s) |
|---|---|
| Control ($n = 25$) | 11.7 (0.7) [8–20] |
| Tongue traction ($n = 24$) | 35.3 (1.5) [25–54]* |
| Berman airway ($n = 24$) | 34.9 (1.6) [25–55]* |

Data were analysed using Student's paired $t$ test (within groups) and analysis of variance (between groups). $P < 0.05$ was deemed significant.

## RESULTS

The three groups were similar in age, weight and sex (table I).

The mean times for successful intubations in the tongue traction group (35.3 s) and in the Berman group (34.9 s) were significantly greater than in the Macintosh group (11.7 s). There was no significant difference between the intubation times of the two fibreoptic groups (table II). Intubation of the trachea in one patient in the tongue traction group could not be completed within the 60 s allowed because of inadequate clearance between the base of tongue and posterior pharyngeal wall. There was also one failure in the Berman group when the tip of the airway entered the left pyriform fossa. As the airway was withdrawn slightly to correct this, obstruction by the tongue became a problem which could not be surmounted within the time allocated. In these two patients, tracheal intubation was performed uneventfully using the Macintosh laryngoscope.

Details of the changes in mean arterial pressures and heart rates within the three groups are summarized in tables III and IV. Analysis of variance showed no significant differences between the three groups before tracheal intubation. Intubation resulted in significant differences between the control group and tongue traction and Berman groups with respect to systolic pressure ($P = 1.3E-7$), diastolic pressure ($P = 6.8E-7$)

TABLE III. *Mean* (SEM) *systolic (SAP) and diastolic (DAP) arterial pressures in control, tongue traction and airway groups.* *$P < 0.05$ *compared with values before intubation*

| Group | Before induction | Before intubation | Time after intubation (min) | | | | |
|---|---|---|---|---|---|---|---|
| | | | 1 | 2 | 3 | 4 | 5 |
| Control ($n = 25$) | | | | | | | |
| SAP (mm Hg) | 121 (3) | 116 (3) | 141 (4)* | 134 (4)* | 122 (3) | 116 (3)* | 113 (2)* |
| DAP (mm Hg) | 70 (2) | 70 (2) | 94 (2)* | 79 (2)* | 73 (2) | 67 (2)* | 64 (2)* |
| Tongue traction ($n = 24$) | | | | | | | |
| SAP (mm Hg) | 116 (2) | 115 (4) | 141 (4)* | 153 (4)* | 138 (4)* | 128 (4)* | 122 (4)* |
| DAP (mm Hg) | 68 (2) | 67 (2) | 97 (3)* | 91 (3)* | 81 (3)* | 76 (3)* | 71 (3) |
| Berman airway ($n = 24$) | | | | | | | |
| SAP (mm Hg) | 120 (3) | 121 (3) | 137 (4)* | 153 (3)* | 140 (4)* | 132 (4)* | 122 (3) |
| DAP (mm Hg) | 69 (2) | 72 (2) | 90 (3)* | 89 (2)* | 79 (2)* | 74 (2)* | 67 (2) |

TABLE IV. *Mean* (SEM) *values of heart rate (beat* $min^{-1}$*) in control, tongue traction and airway groups.* *$P < 0.05$ *compared with values before intubation*

| Group | Before induction | Before intubation | Time after intubation (min) | | | | |
|---|---|---|---|---|---|---|---|
| | | | 1 | 2 | 3 | 4 | 5 |
| Control ($n = 25$) | 80 (2) | 88 (2) | 102 (2)* | 98 (2)* | 95 (2)* | 91 (2) | 88 (2) |
| Tongue traction ($n = 24$) | 76 (2) | 84 (3) | 102 (3)* | 102 (2)* | 101 (3)* | 98 (3)* | 96 (4)* |
| Berman airway ($n = 24$) | 77 (3) | 88 (3) | 99 (4)* | 105 (4)* | 102 (3)* | 100 (4)* | 94 (3)* |

and heart rate ($P = 3.6E-3$). There were no significant differences between the tongue traction and Berman airway groups at any stage.

## DISCUSSION

This study has confirmed a previous report that orotracheal fibreoptic intubation facilitated by direct tongue traction under general anaesthesia takes three times longer to perform than Macintosh intubation [3], even by experienced personnel. While the technical limitations of current instruments and the presence of airway secretions may account for some of this delay, perhaps the most intractable problem is that the base of tongue and epiglottis fall backwards and tend to obstruct the pharyngeal lumen [12,13]. Anterior displacement of the tongue is therefore a vital factor for successful endoscopy in anaesthetized patients. One way of achieving this is by extrusion of the tongue, but an alternative approach is to advance the fibrescope through a modified pharyngeal airway, which not only retracts the tongue anteriorly but also directs the fibrescope towards the larynx. Several types of pharyngeal guide and airway have been described and recommended as useful adjuncts to fibreoptic laryngoscopy [4–8], although there have been no controlled trials to support these claims. We found that, when the Berman airway was used, many of the laryngoscopies were indeed easy. The vocal cords were presented directly ahead of the distal end of the airway and it was simple to advance the laryngoscope into the trachea. However, time was lost in extricating the airway from the pharynx and removing it from around the fibrescope before the intubation could be completed. In a minority of cases, the airway did not come to lie in such a favourable position and either failed to control the tongue and epiglottis satisfactorily or entered one of the pyriform fossae, and on these occasions considerable delay and difficulty were experienced. We therefore conclude that, although the airway may be useful in some fibreoptic intubations, it does not reliably expedite the procedure, as indicated by the finding that the mean intubation time was similar to that required for the tongue traction method and substantially in excess of that of Macintosh intubation.

This investigation has demonstrated that both the controlled tongue traction and the Berman airway methods of fibreoptic intubation caused a significantly greater and more sustained increase in arterial pressure and heart rate than Macintosh intubation. The pressor effects may be related to the extended period of airway intervention which characterizes both these methods of intubation, as Stoelting [11] has demonstrated that increasing the duration of Macintosh laryngoscopy caused a progressive increase in mean arterial pressure. However, it is possible that other mechanisms may also be involved. When examining the effects of laryngoscopy with and without tracheal intubation, Shribman, Smith and Achola [14] observed that Macintosh laryngoscopy alone generated a significant increase in arterial pressure and plasma concentrations of catecholamine, and that tracheal intubation caused little additional response. They suggested, therefore, that tissue tension in the supraglottic region produced by the rigid laryngoscope blade was the major cause of the pressor response. However, this investigation has shown that fibreoptic laryngoscopy and intubation produced a greater pressor response, even though the tongue traction method is associated with little, and the Berman airway with no, increase in supraglottic tissue tension. It is possible, therefore, that superficial stimulation of the pharyngeal mucosa and glottic and tracheal stimulation contribute to the pressor response associated with fibreoptic intubation, particularly as they are applied for an extended period.

Shribman, Smith and Achola [14] reported also that significant increases in heart rate did not occur during Macintosh laryngoscopy alone, but became evident only after intubation of the trachea. This is consistent with earlier work by King and colleagues [15], and implies that glottic and tracheal stimulation may be more important determinants of chronotrophic effects than supraglottic stimulation. This may explain why fibreoptic intubation elicited a greater tachycardia than Macintosh intubation, as insertion of the fibrescope itself into the trachea, in addition to the tracheal tube, may represent a more noxious stimulus. This explanation would also be compatible with the findings of Smith and colleagues [16], who studied the differences between Macintosh and fibreoptic nasotracheal intubation. In this study, the mean fibreoptic intubation time was only 25% greater than mean Macintosh intubation time and the arterial pressure responses were broadly similar, whereas the tachycardia was significantly greater and more sustained in the fibreoptic group.

In conclusion, we observed that the Berman airway appeared to have no advantage over tongue traction with regard to the speed of intubation, and it was not an effective method of attenuating the pressor response to fibreoptic intubation. Anaesthetists should be aware that the cardiovascular disturbances produced by both types of fibreoptic intubation are of an order which may be hazardous in debilitated or frail patients. If fibreoptic techniques are indicated in such patients, awake intubation under local anaesthesia should be considered [17]. Alternatively, in the event of unexpected difficult intubation under general anaesthesia, pharmacological methods should be used to attenuate the pressor response.

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# TRANSPLACENTAL DISTRIBUTION OF ATRACURIUM, LAUDANOSINE AND MONOQUATERNARY ALCOHOL DURING ELECTIVE CAESAREAN SECTION

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## SUMMARY

*Maternal venous (MV), umbilical venous (UV) and umbilical arterial (UA) blood samples were obtained for assay of atracurium, laudanosine and monoquaternary alcohol concentrations in 22 healthy patients undergoing elective Caesarean section under general anaesthesia. At delivery (at a mean time of 8.2 min after atracurium 0.3 mg kg$^{-1}$), the mean UV concentrations were 103 ng ml$^{-1}$ (range 44–189 ng ml$^{-1}$) for atracurium, 26 ng ml$^{-1}$ (range 6–60 ng ml$^{-1}$) for laudanosine and 59 ng ml$^{-1}$ (range 21–148 ng ml$^{-1}$) for monoquaternary alcohol. The ratios of UV:MV, UA:MV and UA:UV blood concentrations were related positively to time since injection of atracurium for all three substances ($P < 0.01$ in each instance). The UV:MV ratio at delivery was greatest for laudanosine: mean 19.4% (range 1–35%), compared with 7% (range 2–21%) for atracurium and 10% (range 0–15%) for monoquaternary alcohol. These low values confirm that, although atracurium crosses the placental barrier and its metabolites may be found in the fetus, the drug is safe to use during Caesarean section.*

**KEY WORDS**

*Anaesthesia: obstetric. Pharmacokinetics: atracurium, laudanosine, monoquaternary alcohol*

It was thought previously that non-depolarizing neuromuscular blocking agents in clinical doses did not cross the placenta [1]—a mistaken view caused probably by the absence of accurate assays for measurement of these drugs in low concentrations [2]. In 1968 it was suggested from a case report that this premise was incorrect [3], and with the advent of improved analytical techniques it is now recognized that all non-depolarizing neuromuscular blocking agents, including tubocurarine [4], pancuronium [5], alcuronium [6] and vecuronium [7] cross the placenta to a degree determined by time and dose. Atracurium has been detected also in umbilical venous blood although, because of the limitations of the assay for this agent at that time, plasma concentrations of less than 50 ng ml$^{-1}$ could not be measured accurately [8]. In addition, umbilical concentrations of the metabolites of atracurium, including the potentially epileptogenic substance laudanosine, have not been reported. With the improved accuracy of detection of atracurium, laudanosine and another metabolite, monoquaternary alcohol (MQA), it is now possible to measure concentrations less than 10 ng ml$^{-1}$ [9, 10]. We have now studied maternal venous (MV), umbilical vein (UV) and umbilical artery (UA) plasma concentrations of these three substances during elective Caesarean section.

## PATIENTS AND METHODS

Following approval by the local Ethics Committee, 22 healthy women undergoing elective Caesarean section under general anaesthesia were asked for their consent for plasma sampling of maternal venous and umbilical venous and arterial blood. All were in good health.

They received a standard anaesthetic in the supine position with a left lateral tilt. After an i.v. infusion was commenced and preoxygenation for

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TABLE I. *Maternal age, weight, time between dose of atracurium 0.3 mg kg$^{-1}$ and delivery and uterine incision to delivery, Apgar scores for the infants at 1 and 5 min and the pH of the umbilical venous (UV) and umbilical arterial (UA) blood (individual values, mean,* SD *and range)*

| Patient No. | Maternal age (yr) | Maternal weight (kg) | Dose–delivery interval (min) | Uterine incision–delivery interval (s) | Apgar score | | pH | |
|---|---|---|---|---|---|---|---|---|
| | | | | | 1 min | 5 min | UV | UA |
| 1 | 31 | 60 | 3.5 | 58 | 9 | 9 | — | 7.29 |
| 2 | 34 | 73 | 10.5 | 110 | 9 | 10 | — | 7.32 |
| 3 | 35 | 91 | 8.75 | 90 | 9 | 10 | 7.25 | — |
| 4 | 26 | 50 | 18.5 | 210 | 5 | 10 | 7.36 | — |
| 5 | 24 | 64 | 4.5 | 80 | 10 | 10 | 7.29 | — |
| 6 | 32 | 85 | 12.75 | 120 | 9 | 10 | 7.29 | 7.24 |
| 7 | 21 | 77 | 9.0 | 90 | 9 | 9 | 7.34 | — |
| 8 | 26 | 87 | 6.7 | 40 | 9 | 10 | 7.31 | 7 27 |
| 9 | 25 | 70 | 6.25 | 45 | 9 | 10 | 7.36 | — |
| 10 | 38 | 76 | 11.25 | 60 | 9 | 9 | 7.34 | 7.32 |
| 11 | 34 | 72 | 6.5 | 45 | 8 | 9 | 7.34 | 7.31 |
| 12 | 25 | 60 | 2.5 | 30 | 9 | 9 | 7.37 | 7.31 |
| 13 | 37 | 97 | 5.2 | 30 | 9 | 9 | 7.33 | 7.3 |
| 14 | 18 | 81 | 4.75 | 60 | 10 | 10 | 7.33 | 7.29 |
| 15 | 31 | 84 | 18.4 | 90 | 8 | 10 | 7.35 | 7.3 |
| 16 | 30 | 72 | 1.25 | 30 | 9 | 10 | 7.37 | — |
| 17 | 22 | 82 | 11.0 | 210 | 5 | 8 | 7.33 | 7.31 |
| 18 | 26 | 78 | 12.25 | 105 | 8 | 9 | 7.31 | 7.29 |
| 19 | 29 | 87 | 3.75 | 60 | 9 | 10 | 7.35 | 7.32 |
| 20 | 34 | 64 | 10.0 | 60 | 5 | 10 | 7.33 | — |
| 21 | 32 | 66 | 7.5 | 60 | 10 | 10 | 7.31 | — |
| 22 | 20 | 77 | 4.75 | 120 | 5 | 10 | 7.21 | 7.25 |
| Mean | 28.6 | 75.1 | 8.2 | 82.0 | 8.3 | 9.6 | 7.3 | 7.3 |
| SD | 5.69 | 11.46 | 4.6 | 50.13 | 1.67 | 0.59 | 0.04 | 0.03 |
| Range | 18–38 | 50–97 | 1.25–18.5 | 30–210 | 5–10 | 8–10 | 7.25–7.37 | 7.24–7.32 |

5 min, cricoid pressure was applied and anaesthesia induced with thiopentone 3–5 mg kg$^{-1}$ and suxamethonium 75–100 mg. The trachea was intubated and anaesthesia maintained with 50% nitrous oxide and 0.8% (inspired) enflurane in oxygen. End-tidal $P\text{CO}_2$ was monitored and maintained at 3–4 kPa. An i.v. cannula was inserted into the arm opposite to the i.v. infusion and 10 ml of blood obtained for measurement of control values. When there was evidence of recovery of neuromuscular function, atracurium 0.3 mg kg$^{-1}$ was given i.v. via the i.v. infusion and the time noted. The time of uterine incision and of delivery of the fetus were also recorded. Another sample of maternal blood (4 ml) was taken from the i.v. cannula immediately before delivery. A 15–20 cm length of doubly clamped umbilical cord was obtained immediately after delivery and samples of umbilical arterial and venous blood were obtained.

The neonate was assessed by the attending paediatrician and the Apgar scores at 1, 5 and 10 min were recorded. The time to onset of spontaneous regular ventilation was noted. The pH of the umbilical vein and arterial samples were measured using a IL BGM 1312 Blood Gas "Manager".

All the blood samples were acidified immediately, centrifuged and the plasma decanted into acidified test tubes before deep-freezing in liquid nitrogen and storage at −20 °C. The plasma was assayed for atracurium, laudanosine and MQA as described previously [9, 10]. The coefficient of variation of the assay for atracurium within the maternal blood range (100–2000 ng ml$^{-1}$) was 5% and within the cord blood range (50–250 ng ml$^{-1}$) 7.5%. Similarly, the coefficient of variation of the laudanosine assay within the maternal range (20–300 ng ml$^{-1}$) was 7.5% and within the cord blood range (10–100 ng ml$^{-1}$) 6%. For MQA, the coefficient of variation was 8% for both maternal blood range (100–1000 ng ml$^{-1}$) and cord blood range (20–250 ng ml$^{-1}$). The lower limits of detection of the assay were 5 ng ml$^{-1}$ for atracurium, 2 ng ml$^{-1}$ for laudanosine and 10 ng ml$^{-1}$ for MQA.

TABLE II. *Plasma concentrations of atracurium, laudanosine and monoquaternary alcohol (MQA) in maternal vein (MV), umbilical vein (UV) and umbilical artery (UA) for the 22 patients at delivery (individual values, mean,* SD *and range)*

| Patient No. | Atracurium (ng ml$^{-1}$) | | | Laudanosine (ng ml$^{-1}$) | | | MQA (ng ml$^{-1}$) | | |
|---|---|---|---|---|---|---|---|---|---|
| | MV | UV | UA | MV | UV | UA | MV | UV | UA |
| 1 | 2300 | 104 | 15 | 117 | 23 | 0 | 486 | 21 | 0 |
| 2 | 1180 | 189 | 142 | 116 | 30 | 12 | 484 | 72 | 50 |
| 3 | 1400 | 147 | 108 | 171 | 23 | 10 | 569 | 55 | 34 |
| 4 | 593 | 72 | 46 | 148 | 27 | 9 | 417 | 79 | 56 |
| 5 | 2138 | 74 | 30 | 150 | 29 | 4 | 486 | 56 | 19 |
| 6 | 1301 | 69 | — | 88 | 23 | — | 421 | 53 | — |
| 7 | 1271 | 113 | 37 | 128 | 35 | 8 | 544 | 68 | 35 |
| 8 | 1911 | 85 | 39 | 98 | 21 | 3 | 523 | 56 | 24 |
| 9 | 1207 | 44 | 25 | 125 | 28 | 12 | 474 | 44 | 31 |
| 10 | 1387 | 96 | 70 | 125 | 28 | 12 | 665 | 84 | 58 |
| 11 | 1538 | 103 | 70 | 72 | 22 | 9 | 531 | 64 | 46 |
| 12 | 2485 | 51 | 8 | 126 | 13 | 2 | 524 | 21 | 10 |
| 13 | 2687 | 116 | 29 | 242 | 26 | 5 | 902 | 58 | 22 |
| 14 | 1784 | 138 | 46 | 219 | 22 | 0 | 719 | 60 | 18 |
| 15 | 721 | 148 | 107 | 145 | 58 | 35 | 605 | 148 | 122 |
| 16 | 4920 | 103 | 47 | 487 | 6 | 0 | 1114 | — | 15 |
| 17 | 1705 | 131 | 82 | 91 | 25 | 9 | 562 | 74 | 39 |
| 18 | 1501 | 117 | — | 170 | 60 | — | 628 | 84 | — |
| 19 | 2474 | 63 | 36 | 240 | 26 | 0 | 931 | 38 | 16 |
| 20 | 1662 | 93 | 65 | 163 | 21 | 4 | 666 | 36 | 21 |
| 21 | 1293 | 81 | 45 | 134 | 9 | 0 | 533 | 41 | 0 |
| 22 | 2788 | 117 | 52 | 117 | 14 | 0 | 586 | 36 | 0 |
| Mean | 1829 | 103 | 55 | 158 | 26 | 7 | 608 | 59 | 31 |
| SD | 911.3 | 35.0 | 33.8 | 86.4 | 12.7 | 8.1 | 173.9 | 27.5 | 27.8 |
| Range | 593–4920 | 44–189 | 8–142 | 72–487 | 6–60 | 0–35 | 417–1114 | 21–148 | 0–122 |

The ratios UV:MV, UA:MV and UA:UV were calculated for atracurium, laudanosine and MQA. UV:MV and UA:MV give an index of the degree of placental transfer, whilst the UA:UV ratio may be used to give an index of the extent of fetal equilibration of the three substances [11]. The three ratios for atracurium, laudanosine and MQA were plotted against time.

The relationship between the UV:MV, UA:MV and UA:UV ratios for atracurium, laudanosine and MQA and the time from administration of atracurium were analysed using Spearman's rank correlation coefficient. The significance of the resulting values was determined from standard tables [12]. $P < 0.05$ was considered significant.

## RESULTS

The times from administration of atracurium to delivery of the fetus (range 1.25–18.5 min) and the times from uterine incision to delivery (range 30–210 s) are shown in table I, with maternal ages and weights and 1- and 5-min Apgar scores; the Apgar score in all the babies at 10 min was 10. The time to onset of spontaneous regular ventilation was less than 30 s in all babies.

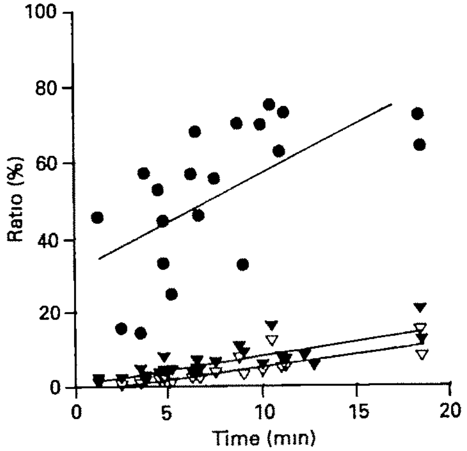

FIG. 1. Ratio of UV:MV (▼), UA:MV (▽) and UA:UV (●) plasma concentrations of atracurium for the 22 patients at delivery, with lines of identity. $r_s = 0.76$, $P < 0.002$; $r_s = 0.61$, $P < 0.01$, $r_s = 0.69$, $P < 0.002$, respectively.

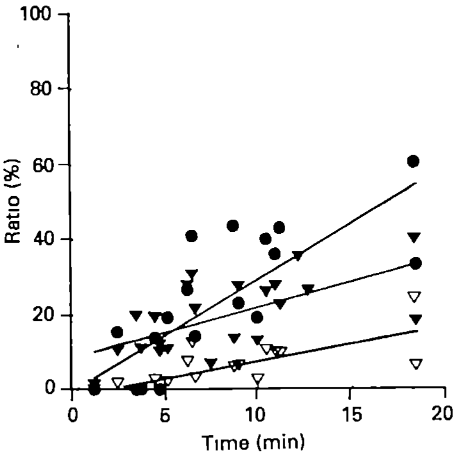

FIG. 2. Ratio of UV:MV (▼), UA:MV (▽) and UA:UV (●) plasma concentrations of laudanosine for the 22 patients at delivery, with lines of identity. $r_s = 0.6$, $P < 0.01$; $r_s = 0.75$, $P < 0.002$; $r_s = 0.77$, $P < 0.002$, respectively.

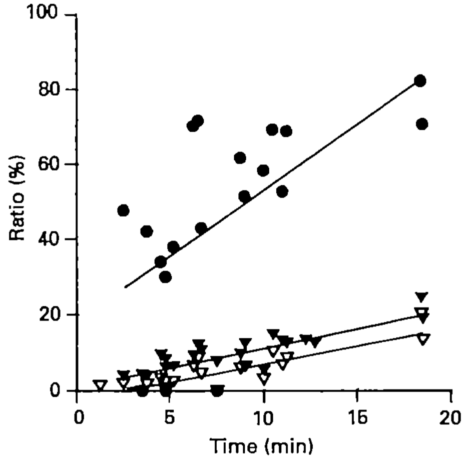

FIG. 3. Ratio of UV:MV (▼), UA:MV (▽) and UA:UV (●) plasma concentrations of MQA for the 22 patients at delivery, with lines of identity. $r_s = 0.87$, $P < 0.002$; $r_s = 0.77$, $P < 0.002$; $r_s = 0.64$, $P < 0.01$, respectively.

The MV, UV and UA concentrations of atracurium, laudanosine and MQA are shown in table II, and the ratios UV:MV, UA:MV and UA:UV for atracurium, laudanosine and MQA in each patient are plotted against time from administration of atracurium to delivery of the fetus in figures 1–3. For all three substances, the three ratios of the two plasma concentrations correlated significantly with the time between administration of atracurium and delivery. The mean (SD) ratios in the 22 patients of UV:MV, UA:MV and UA:UV, for atracurium, laudanosine and MQA at delivery are given in table III.

## DISCUSSION

Although water soluble, highly ionized drugs such as non-depolarizing neuromuscular blocking agents are not expected to cross lipid membranes such as the placenta, it is probable that the non-protein bound fraction of these quaternary ammonium compounds gradually passes across this barrier [11]. The speed at which this occurs is thought to be related in part to the permeability of the placenta and the blood flow to it, both of which may be altered in disease states. It must be accepted, therefore, that significant patient variation is likely to occur in the degree of placental transmission of neuromuscular blocking agents, especially during emergency Caesarean section. For this reason, this study was limited to those patients undergoing elective Caesarean section who were not suffering from any disease states known to affect placental blood flow, such as diabetes mellitus or pre-eclampsia.

In the short time between induction and delivery, equilibration of atracurium, laudanosine and MQA would not be expected to have occurred between maternal venous and umbilical venous blood and this is confirmed by our results (tables II, III). The UV:MV ratios reported for other neuromuscular blocking drugs at delivery of the fetus vary between 11 % for vecuronium [7], 12 % for tubocurarine [4] and 22 % for pancuronium [5]. These data suggest that atracurium, with a mean ratio of 7 %, may cross the placenta at a somewhat slower rate than the other non-depolarizing neuromuscular blocking agents, but generalizations are difficult because of the differences in time. The UV values in this study, in the range 44–189 ng $ml^{-1}$, are broadly similar to those reported by Flynn, Frank and Hughes in 1984 [8]. It is not yet clear if UV, or UA, plasma concentrations are the more relevant when considering the potential effect of a neuromuscular blocking agent on the fetus. The umbilical arteries are branches of the common iliac arteries, which represent the continuation of the aorta. In the neonate, it is the descending aorta which supplies the majority of the somatic musculature. It would seem logical, therefore, to assume that it is the UA values which approximate more closely to those found at the neuromuscular junction. In our

TABLE III. *Mean,* SD *and ranges of the ratio (%) of umbilical vein:maternal vein (UV:MV), umbilical artery:maternal vein (UA:MV) and umbilical artery:umbilical vein (UA:UV) concentrations of atracurium, laudanosine and monoquaternary alcohol (MQA) on delivery of the fetus*

| | Atracurium | | | Laudanosine | | | MQA | | |
|---|---|---|---|---|---|---|---|---|---|
| | UV:MV | UA:MV | UA:UV | UV:MV | UA:MV | UA:UV | UV:MV | UA:MV | UA:UV |
| Mean (%) | 7.0 | 4.1 | 52.8 | 19.4 | 5.2 | 21.4 | 10.0 | 5.4 | 49.6 |
| SD (%) | 4.5 | 4.5 | 3.8 | 18.6 | 9.7 | 6.0 | 18.5 | 5.1 | 23.3 |
| Range (%) | 2–21 | 0.3–12 | 14–75 | 1–35 | 0–24 | 0–60 | 0–15 | 0–20 | 0–82 |

study, the mean (SD) UA value for atracurium was 55 (33.8) ng ml$^{-1}$. Fisher and colleagues [13] demonstrated that the plasma atracurium concentration required to produce 50% neuromuscular block in infants aged 4–11 months was 363 (118) ng ml$^{-1}$. Our results suggest that the doses of atracurium used routinely during Caesarean section are unlikely to result in significant neuromuscular block in the neonate.

Several factors affect the UV concentrations of the metabolites of atracurium. As both metabolites have a lower molecular weight than the parent compound, they cross the placenta more easily [11]. As laudanosine is, in addition, more lipid soluble than atracurium or MQA, of the three substances it might be expected to cross the placenta most rapidly. It is not surprising, therefore, that the UV:MV ratios were greater for the two metabolites than for the parent drug, with that of laudanosine being the greatest, at 19.4% (table III). This may cause particular concern, as laudanosine is known to be epileptogenic in animals [14]. The concentration of laudanosine in the central nervous system, which is determined by the laudanosine concentration in the cerebral blood supply, is the important factor in this respect. In the fetus, the cerebral circulation receives a preferential supply of oxygenated blood returning via the UV. This flows via the inferior vena cava, through the foramen ovale, into the ascending aorta and thence to the carotid arteries. Thus, in contrast to the degree of neuromuscular block produced, the central nervous system laudanosine concentration may be determined more accurately by meauring the UV rather than the UA concentrations. In this study, the mean UV plasma concentration of laudanosine was 26 (13) ng ml$^{-1}$. These values would not be expected to produce side effects in adult humans, and the maternal venous concentrations of less than 500 ng ml$^{-1}$ would not cause symptoms, the toxic values in dogs being more than 14000 ng ml$^{-1}$ [14]. It must be stressed, however, that the toxic concentration of laudanosine in the human neonate is unknown.

It is also interesting that, although the UV:MV ratios are greatest for the more lipid soluble laudanosine, the UA:UV ratios are smaller for this substance than for the more water soluble atracurium and MQA. It would be inappropriate to suggest that, in such a short time as 8 min, this smaller UA:UV ratio is caused by fetal excretion of laudanosine, even though it is recognized that the fetus may excrete drugs through the liver and kidney [11] and it is thought that laudanosine is excreted in part by these routes in adults [15, 16]. We feel that this finding may be explained only by the larger volume of distribution of the more lipid soluble laudanosine, which has already been demonstrated, although only in adults [9, 15].

The mean UV:MV ratio of 10% for MQA is also in keeping with its molecular weight and known water solubility. Vandenbrom and colleagues [17] demonstrated recently that peak plasma MQA concentrations in healthy adults after a bolus dose of atracurium 0.5 mg kg$^{-1}$ were of the order of 1000 ng ml$^{-1}$. The greatest MV value detected in this study after a smaller dose of atracurium was similar—1114 ng ml$^{-1}$. The greatest UV value, however was only 148 ng ml$^{-1}$. No toxic effects of MQA have been documented yet and it is therefore unlikely that the concentrations detected in the fetal plasma in this study have any detrimental effect.

## ACKNOWLEDGEMENT

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*British Journal of Anaesthesia* 1991; **66**: 557–561

# PHARMACOKINETICS AND PHARMACODYNAMICS OF ATRACURIUM WITH AND WITHOUT PREVIOUS SUXAMETHONIUM ADMINISTRATION

F. DONATI, S. S. GILL, D. R. BEVAN, J. DUCHARME, Y. THEORET AND F. VARIN

## SUMMARY

*Suxamethonium increases neuromuscular block produced by non-depolarizing agents administered subsequently. To determine if this effect has a pharmacokinetic or pharmacodynamic origin, 18 ASA physical status I or II adults received atracurium 0.2 mg kg*$^{-1}$*, with (*n *= 10) or without (*n *= 8) previous injection of suxamethonium 1 mg kg*$^{-1}$*, during a thiopentone–nitrous oxide–isoflurane (0.5% end-tidal) anaesthetic. Arterial blood samples were obtained and plasma atracurium concentration measured by HPLC. Train-of-four stimulation was applied to the ulnar nerve and the force of contraction of the adductor pollicis muscle was recorded. Mean (*SEM*) volume of distribution was slightly greater with previous suxamethonium (143 (13) ml kg*$^{-1}$*) than without (109 (5) ml kg*$^{-1}$*) (*$P < 0.04$*). Mean elimination half-life was unaffected (20.3 (0.8) min and 20.4 (1.6) min, respectively). Neuromuscular block was more intense and recovery was slower with previous administration of suxamethonium. Atracurium concentration at 50% block (*$Cp^{ss}_{50}$*) was 305 (30) ng ml*$^{-1}$* with and 454 (25) ng ml*$^{-1}$* without previous suxamethonium (*$P < 0.01$*). It is concluded that suxamethonium may be associated with a slight increase in the volume of distribution of atracurium, but this effect is more than compensated by a decrease in atracurium concentration required for a given effect.*

### KEY WORDS

*Drug interactions atracurium, suxamethonium Pharmacodynamics: atracurium. Pharmacokinetics atracurium. Neuromuscular relaxants · atracurium, suxamethonium*

The neuromuscular effect of non-depolarizing agents is affected by previous administration of suxamethonium. A single dose of pancuronium [1, 2], vecuronium [2–5] or atracurium [6] has been reported to produce more intense block if given after suxamethonium. A shift to the right of the dose–response curve of vecuronium [3] has been described with previous administration of suxamethonium. The duration of this effect is at least 30 min [4] and possibly as long as 2 h or more [2].

Such a change in the relationship between dose and effect could be caused by a pharmacokinetic or pharmacodynamic alteration, or both. To determine quantitatively the role of each in the changes caused by suxamethonium, plasma concentrations should be measured and correlated with effect. Moreover, there are no comparative data on the pharmacokinetics of non-depolarizing blocking drugs with and without previous administration of suxamethonium.

The purpose of this study was to determine the pharmacokinetics of atracurium together with its pharmacodynamics (neuromuscular effect), with and without previous administration of suxamethonium.

## PATIENTS AND METHODS

The study was approved by the Hospital Ethics Committee and informed consent was obtained

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from each subject. We studied 18 ASA physical status I and II adult patients, aged 19–75 yr, undergoing elective surgery for which arterial cannulation was indicated. Patients with cardiovascular, pulmonary, neuromuscular, hepatic or renal disease were excluded. Other exclusion criteria included anaemia, a history of multiple allergies, and concurrent administration of drugs known or suspected to interfere with neuromuscular function. Patients who deviated from their ideal body weight by more than 20% were also excluded.

The patients were premedicated with diazepam 5–10 mg orally or a combination of pethidine 50–70 mg i.m. and atropine 0.4–0.6 mg i.m. On arrival of the patient in the operating room, ECG, haemoglobin oxygen saturation and arterial pressure were measured. Anaesthesia was induced with fentanyl 2–5 $\mu$g kg$^{-1}$ and thiopentone 4–7 mg kg$^{-1}$, and maintained with 70% nitrous oxide and 0.5% end-tidal isoflurane in oxygen, and fentanyl as required. In eight patients, the lungs were ventilated manually via a mask until atracurium had been given. Suxamethonium 1 mg kg$^{-1}$ was given i.v. to the other 10 subjects, tracheal intubation was performed and mechanical ventilation of the lungs commenced. An arterial cannula was inserted into the left radial artery.

The left ulnar nerve was stimulated supramaximally via silver–silver chloride electrodes applied to the skin at the elbow. The force of contraction of the adductor pollicis muscle was recorded using a Grass FT-10 force transducer. Train-of-four stimulation (2 Hz for 2 s) with impulses of 0.2 ms in duration was repeated every 12 s.

After a stable baseline had been obtained (or, in patients who received suxamethonium, after 100% T1 recovery from neuromuscular block), atracurium 0.2 mg kg$^{-1}$ was given as a rapid i.v. bolus. In patients who did not receive suxamethonium, tracheal intubation was performed after injection of atracurium, when maximal twitch depression was observed. All patients underwent mechanical ventilation of the lungs. The end-tidal carbon dioxide was measured with a mass spectrometer (SARA) and maintained within normal limits. When first twitch height (T1) returned to 50% or more of control, surgical relaxation was continued with vecuronium.

Arterial blood samples (3 ml) were drawn into heparinized syringes at 0, 0.5, 1, 1.5, 2, 3, 5, 7, 10, 15, 20, 30, 45, 60, 90 and 120 min. The samples were transferred immediately into glass tubes which were placed in ice for approximately 5 min. The samples were centrifuged, acidified to pH 4–5 with sulphuric acid 2 mol litre$^{-1}$ and frozen.

Plasma concentrations of atracurium and laudanosine were measured by a specific HPLC assay with fluorimetric detection [7]. Plasma samples (250 $\mu$l) enriched with verapamil 250 ng (internal standard) were reacidified with 10 $\mu$l of sulphuric acid 0.5 mol litre$^{-1}$. The plasma proteins were precipitated with acetonitrile. After centrifugation, an aliquot of the supernatant was injected directly into the HPLC system. Atracurium and metabolites were separated with a Hichrom Spherisorb $C_8$ column (100 × 4.6 mm i.d., 5-$\mu$m particle size; Reading, U.K.) using a linear gradient for the mobile phase (pH 5) at a flow rate of 1.7 ml min$^{-1}$. The mobile phase changed from 100% of 0.03-M phosphate buffer–methanol–acetonitrile (57.5:5:37.5) to 100% of 0.1-M phosphate buffer–methanol–acetonitrile (47.5:15:37.5) in 8 min. The Shimadzu fluorescence detector (Kyoto, Japan) excitation and emission wavelengths were set at 240 nm and 320 nm, respectively. The method was sensitive for concentrations greater than 20 ng ml$^{-1}$, the mean coefficient of variation was less than 5%, and linearity was present in the range 30–8000 ng ml$^{-1}$ for both atracurium and laudanosine. Vecuronium did not interfere with the measurement of either atracurium or laudanosine.

The plasma concentration values of atracurium were fitted to a two-compartment mamillary model. Pharmacokinetic–pharmacodynamic correlations were also made by calculating a value for $k_{e0}$ using a non-parametric link model [8]. A sigmoid *E*max model was used to fit effect, measured as T1 depression, with effect compartment concentration, providing values for the concentration corresponding to 50% block ($C_{\mathrm{P}}^{ss}{}_{50}$) and for the slope of the relationship ($\gamma$) [9]. Siphar software (SIMED, France) was used to fit these data.

TABLE I. *Patient characteristics (mean (range or* SEM*))*

| | Suxamethonium | No suxamethonium |
|---|---|---|
| Number | 10 | 8 |
| Sex (M/F) | 6/4 | 4/4 |
| Age (yr) | 52 (25–64) | 56 (26–68) |
| Weight (kg) | 61 (3) | 65 (4) |

Table II. *Neuromuscular block (mean (SEM)).* *P < *0.05 between groups*

| | Suxamethonium | | No suxamethonium |
|---|---|---|---|
| Maximum block (%) | 95.2 (2.0) | * | 85 1 (3.8) |
| Time to max. block (min) | 5.7 (0.6) | * | 9.5 (0.8) |
| Time to 25% recovery (min) | 24.6 (2.9) | * | 16.4 (2.1) |
| Time to 50% recovery (min) | 31.8 (3.0) | * | 24.0 (1.6) |

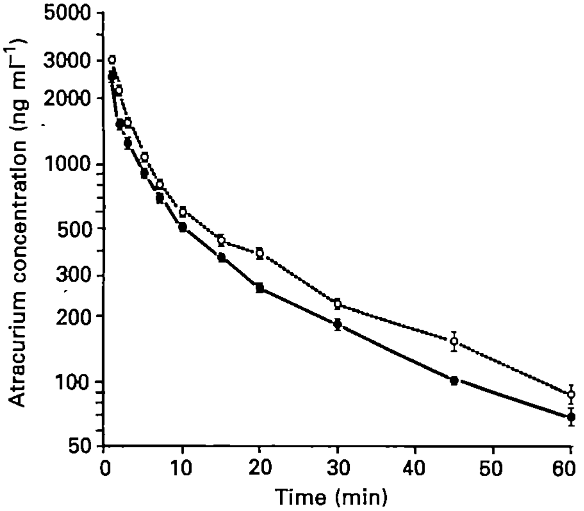

Fig. 1. Plasma concentrations of atracurium, after a bolus injection of 0.2 mg kg$^{-1}$ with (●) and without (○) previous administration of suxamethonium 1 mg kg$^{-1}$.

Unless specified otherwise, the results are presented as mean (SEM). Between-group comparisons were made using Student's *t* test. $P \leqslant 0.05$ was considered significant.

## RESULTS

Both groups were comparable in age, sex and weight (table I).

Table IV. *Pharmacokinetic–pharmacodynamic relationships (mean (SEM)).* *P < *0.05 between groups*

| | Suxamethonium | | No suxamethonium |
|---|---|---|---|
| $C_P{}^{ss}{}_{50}$ (ng ml$^{-1}$) | 305 (30) | * | 454 (25) |
| γ (logit log$^{-1}$) | 5.56 (0.54) | | 6.08 (0.68) |
| $k_{eo}$ (min$^{-1}$) | 0.091 (0.012) | | 0.068 (0.007) |

Maximum neuromuscular block was greater in patients who had received suxamethonium, and recovery times were longer (table II). Time to maximum block was the same in both groups.

At all times, the arterial plasma concentration of atracurium was slightly greater in patients who did not receive suxamethonium (fig. 1). There was no difference in mean residence time (MRT) or elimination half-lives. The volume of central compartment, volume of distribution at steady state and volume calculated according to the area under the curve ($V^\beta$) were greater (expressed per kg body weight) in patients who had received suxamethonium (table III). Clearance (*Cl*) was also slightly greater in patients who had received suxamethonium (table III).

Pharmacokinetic–pharmacodynamic modelling indicated that the concentration required for 50% block ($C_P{}^{ss}{}_{50}$) was approximately 50% greater in patients who did not receive suxamethonium (table IV). The slope of the effect–concentration

Table III. *Pharmacokinetic variables (mean (SEM)). MRT = Mean residence time*; $V^\beta$ = *volume of distribution calculated according to area under the curve*; $V^{ss}$ = *volume of distribution at steady state*; $V_C$ = *volume of central compartment*; $T_{\frac{1}{2}}{}^\alpha$, $T_{\frac{1}{2}}{}^\beta$ = *half-lives*; Cl = *clearance.* *P < *0.05 between groups*

| | Suxamethonium | | No suxamethonium |
|---|---|---|---|
| MRT (min) | 21.1 (0.8) | | 21.9 (1.6) |
| $V^\beta$ (ml kg$^{-1}$) | 195 (16) | * | 145 (8) |
| $V^{ss}$ (ml kg$^{-1}$) | 143 (13) | * | 109 (5) |
| $V_C$ (ml kg$^{-1}$) | 63 (6) | * | 41 (2) |
| $T_{\frac{1}{2}}{}^\alpha$ (min) | 2.59 (0.13) | * | 2.01 (0.21) |
| $T_{\frac{1}{2}}{}^\beta$ (min) | 20.3 (0.8) | | 20.4 (1.6) |
| *Cl* (ml kg$^{-1}$ min$^{-1}$) | 6 6 (0.5) | * | 5.0 (0.2) |

relationship ($\gamma$) was similar in both groups and the rate constant ($k_{eo}$) for equilibrium with the neuromuscular junction was not statistically different between groups (table IV).

The sampling period was too short to carry out the pharmacokinetic analysis of laudanosine. Initial laudanosine concentrations were 3–10% of corresponding atracurium concentrations, suggesting that blood sampling was associated with little spontaneous degradation.

## DISCUSSION

This study has demonstrated that the concentration corresponding to 50% atracurium block ($C_{P}^{ss}{}_{50}$) was decreased by previous administration of suxamethonium. In addition, the pharmacokinetics of atracurium were affected slightly by administration of suxamethonium. Elimination half-life of atracurium was not affected by suxamethonium administration, but the volume of central compartment and volume of distribution were increased by 20–30%. These pharmacokinetic changes were associated with smaller plasma concentrations, which tended to diminish the dynamic changes. The net result was a small but significant increase in neuromuscular block and time to 50% recovery.

In this study, atracurium concentrations were measured in arterial blood, not in peripheral venous blood as in most other studies [10–18]. This method is probably more accurate, as arterial blood is mixed and large differences may occur between venous concentrations, depending on the site of sampling [19]. This is especially true of early samples, when tissue uptake is most important. This may explain why the volume of distribution $V^{\beta}$ obtained in this study in patients who did not receive suxamethonium (145 ml kg$^{-1}$) is at the lower end of the range reported previously (142–202 ml kg$^{-1}$) [10–18]. Similarly $k_{eo}$, or rate of transfer of drug into effect compartment, was less in the present (0.068 min$^{-1}$) than in previous studies (0.1 and 0.074 min$^{-1}$) [12, 17]. This again may be explained by the greater arterial concentrations in early samples. The distribution (2.01 min) and terminal (20.4 min) half-lives were similar to those reported previously (2–3 min and 17–21 min, respectively) [10–18].

The dose of 0.2 mg kg$^{-1}$ was chosen in this study because it approximates to $ED_{90}$–$ED_{95}$ [20]. Therefore, a large number of blood samples could be obtained during both onset and offset of neuromuscular block, so that a better estimate of the kinetic–dynamic relationship could be obtained. In addition, small doses are associated with rapid recovery. Thus the sensitivity of the neuromuscular junction to atracurium was probably unchanged during recovery compared with onset. If such an alteration occurred, the present kinetic–dynamic analysis would be less reliable. However, the effects of suxamethonium on subsequent non-depolarizing block may last up to 2 h [2], much longer than the time to 50% recovery (31 min in this study). The problem associated with using a small dose was the relatively small plasma concentrations of atracurium, especially 2 h after injection. However, reliable measurements of plasma concentrations could be made until 90 min, or four to five times the terminal half-life.

The results of the kinetic–dynamic analysis suggest that, in the absence of previous administration of suxamethonium, the plasma concentration at steady state for a given degree of block may be increased by 50% compared with atracurium given after suxamethonium. In the present study, the $C_{P}^{ss}{}_{50}$ might have been reduced by administration of isoflurane, but both groups received the same concentration (0.5% end-tidal).

The present study suggests that administration of suxamethonium may be associated with small changes in atracurium kinetics. Distribution volume and clearance increased by 25–30% when suxamethonium had been given. Such alterations may be caused by suxamethonium-induced modification in the binding of atracurium to plasma proteins, red blood cells, or extravascular tissue. As suxamethonium may cause long-lasting dynamic changes at the neuromuscular junction, probably via an interaction with a receptor, a modification of other proteins is possible. The extent of binding of atracurium to plasma proteins is appreciable [17], and its affinity for extravascular tissue is not known. Suxamethonium, which produces hyperkalaemia, could also produce fluid shifts. It is not known if these changes last long enough to modify the distribution of drugs administered subsequently. Irrespective of the mechanism, these kinetic changes are small, and do not offset completely the dynamic changes. However, it is recommended that, for pharmacokinetic studies, administration of suxamethonium is standardized, because the use of this drug in some patients would be an unnecessary source of variation.

The main effect of administration of suxamethonium on subsequent atracurium block is a shift of the effect–concentration relationship to the left. In other words, smaller concentrations produce the same neuromuscular effect. The mechanism for this relatively long lasting potentiating effect is not known. However, this study suggests that this may be caused by an increase in end-plate sensitivity to atracurium. Clinically, less atracurium is required for an equivalent degree of block if suxamethonium has been used previously.

## ACKNOWLEDGEMENT

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# CENTRAL ENHANCEMENT OF EVOKED ELECTROMYOGRAPHIC MONITORING OF NEUROMUSCULAR FUNCTION†

D. C. SMITH

**SUMMARY**

*Central neural influences on neuromuscular transmission may explain the frequent failure of evoked electromyographic (EEMG) responses to return to control values during offset of neuromuscular block. This study, performed in conscious subjects, did not demonstrate any change in EEMG response of either the first dorsal interosseous muscle during onset of ulnar nerve block or the flexor hallucis brevis during onset of subarachnoid block. It is concluded that central enhancement of EEMG response via a neural mechanism does not explain the observed failure of EEMG monitoring of neuromuscular block.*

**KEY WORDS**

*Measurement techniques. electromyography. Neuromuscular transmission*

Evoked electromyographic (EEMG) monitoring of neuromuscular block during anaesthesia produces unreliable results in 5–42% of cases [1–3]. This is usually because of a failure of the first response of the train-of-four to return to the control value during offset of neuromuscular block, although the response occasionally returns to values greater than control. The reasons for this are unclear, but one possible explanation is the modification during anaesthesia of a central mechanism responsible for "muscle reactivity" [4]. This hypothesis has not been subject to experimental validation, in spite of its potential importance. Central enhancement of EEMG has been quoted as an explanation for the failure of EEMG monitoring [2, 3], although the neuroanatomical basis for the effect has not been defined.

This study was designed to test this hypothesis.

## SUBJECTS AND METHODS

The study of Paloheimo and Rantala [4] was repeated in so far as the brief details in the report would permit. Electromyographic monitoring was performed using two Datex NMT100 Relaxographs; both machines gave identical responses on an electronic EEMG simulator and stimulus current monitor. The skin at the monitoring site was prepared by rubbing vigorously for 30 s with a gauze soaked in isopropyl alcohol. The Relaxographs were attached to the monitoring site via foam-based electrodes (Nikomed 4570); these electrodes have been found to be better than the electrodes supplied with the Relaxograph, producing stable EEMG records with minimal movement-related artefact [author's unpublished observations]. The Relaxograph leads were taped with "Micropore" to the limb being monitored in order to reduce artefact from cable stresses. Calibration of the Relaxographs was performed in all cases with the subject awake, before any intervention. A supramaximal response was achieved in all subjects before the study began.

### *Volunteer study*

Five adult males agreed to participate in this investigation. All were ASA I, devoid of neuromuscular disease and not receiving any medication. Electromyographic monitoring was performed on both arms; stimulation of the ulnar

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nerves at the wrist produced responses recorded over the first dorsal interosseous muscles. In order to reduce movement artefact, each hand was held in a fist, thumb on the outside, by a piece of 10-cm adhesive strapping. The elbows were supported on cushions with the forearms resting on the volunteer's chest. This position allowed easy access to the ulnar nerves at the elbow, without disturbing the EEMG monitoring. Both Relaxographs were calibrated and recordings of the EEMG were made from both arms for 10 min. Subsequently, an ulnar nerve block was performed at one elbow using 6 ml of 2% lignocaine with adrenaline 1:200000 (Xylocaine with adrenaline, Astra). This volume and concentration were chosen to ensure a dense sensory and motor block of the ulnar nerve. Recordings of EEMG from both arms were continued for 30 min after the nerve block.

### *Patient study*

Twenty patients undergoing transurethral resection of the prostate under subarachnoid block were visited the night before surgery; supramaximal stimulation of the posterior tibial nerve was demonstrated and verbal consent for the study was obtained. Only 15 patients were enrolled into the study because five declined to participate after the demonstration of nerve stimulation. Premedication with temazepam 10–20 mg was administered 90–120 min before operation. Electromyographic monitoring was performed on the left leg: stimulation of the posterior tibial nerve at the medial malleolus produced a response recorded over the flexor hallucis brevis. The Relaxograph was calibrated and a control recording made for 5 min. The patient was turned to the left lateral position for induction of subarachnoid block, which was achieved with 0.5% bupivacaine in 8% glucose 3.5 ml (Marcain heavy, Astra) injected at the L2–3 or L3–4 interspace. Patients were returned immediately to the supine position and the recording was continued for a further 30 min, or until surgery was completed.

## RESULTS

Clinically complete motor and sensory paralysis of the ulnar nerve was obtained in all five volunteer subjects; although the sensation of nerve stimulation did not disappear on the blocked side, its intensity was diminished mildly. In the patient group, a clinically complete, bilateral motor and sensory block was produced to at least T10 in every individual; the subjects ceased to feel the nerve stimuli 10–15 min after induction of the subarachnoid block.

TABLE I. *Time trends of the first EEMG response to the train-of-four during onset of subarachnoid anaesthesia in the 15 patients studied. Values represent the mean of four consecutive responses. — = Value not obtained because the operation was completed. Numbers in parentheses are 95% confidence intervals for the mean, based upon Student's* t *distribution*

| Patient | Control value | Time from subarachnoid injection (min) | | |
|---|---|---|---|---|
| | | 0 | 15 | 30 |
| MMD | 99 | 96 | 100 | 99 |
| TDF | 101 | 103 | 100 | 96 |
| LF | 100 | 100 | 99 | 96 |
| DC | 98 | 98 | 98 | 98 |
| TJH | 98 | 98 | 98 | 98 |
| FHW | 101 | 99 | 100 | 99 |
| ED | 99 | 100 | 95 | 91 |
| JG | 102 | 86 | 121 | — |
| JH | 100 | 100 | 97 | 94 |
| GH | 103 | 106 | 105 | — |
| LR | 98 | 99 | 97 | — |
| JB | 99 | 102 | 103 | — |
| CGT | 99 | 89 | 100 | — |
| RF | 102 | 107 | 100 | 100 |
| FW | 106 | 130 | 130 | 130 |
| Mean | 100 (1.2) | 101 (5.4) | 103 (5.4) | 100 (7.6) |

Table I shows the EEMG responses measured during the patient study. There was no change in the EEMG response during onset of conduction block in each of the study groups, and no change in EEMG response in the control arms of the volunteers. Three patients (J.G., C.G.T. and F.W.) exhibited changes in EEMG response related to movement during positioning for lumbar puncture (fig. 1). These changes were abrupt, and temporally related to changes in position.

## DISCUSSION

In contrast with the work of Paloheimo and Rantala [4], this investigation has not demonstrated any change in the EEMG response during onset of either subarachnoid block or ulnar nerve block. In their abstract, Paloheimo and Rantala suggested that complete motor block (defined as abolition of spontaneous EMG activity) was required to demonstrate the full effect of central enhancement. Assessment of the spontaneous

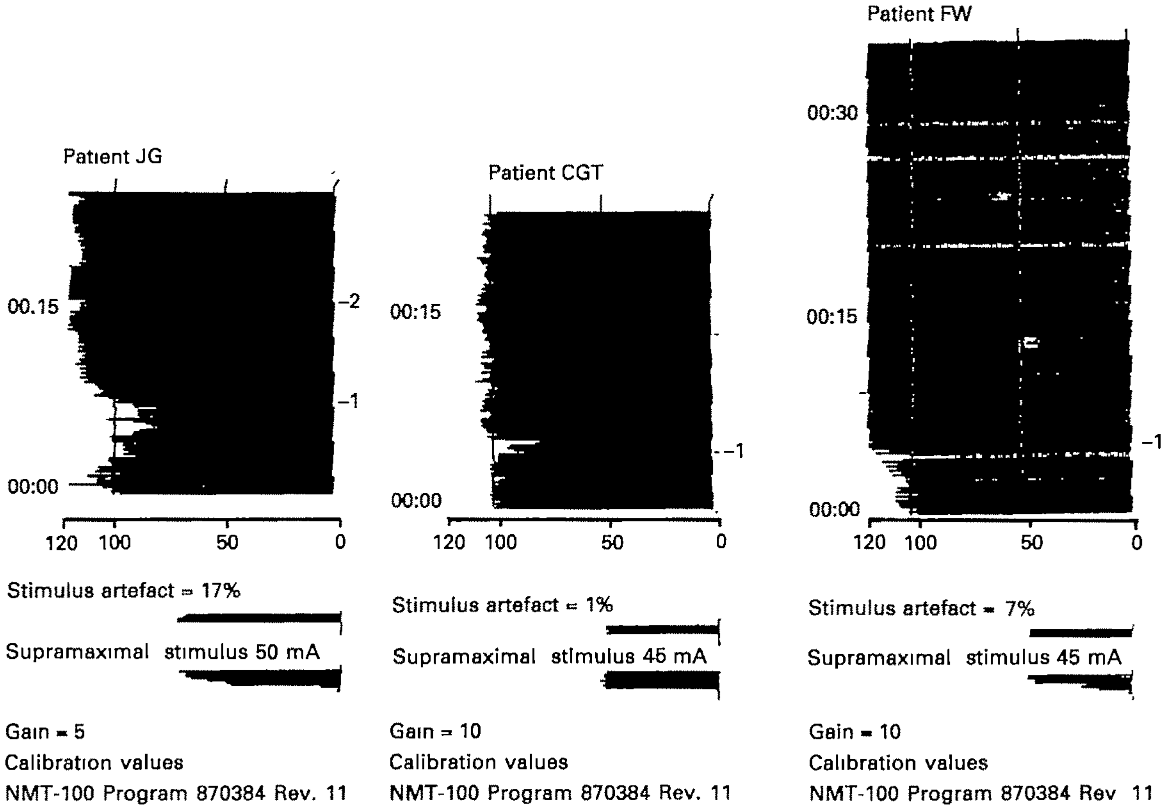

FIG. 1. EEMG records from three patients demonstrating movement-related artefacts. Marker 1 in each record indicates the subarachnoid injection of bupivacaine.

EMG was not available for the study reported here. However, the nerve conduction blocks were complete clinically, and this study has not demonstrated any central enhancement effect. The lack of agreement with the observations of Paloheimo and Rantala requires discussion.

The experimental details in the original abstract were brief, but there were small differences in methodology between the two studies [Paloheimo M., personal communication].

*Electrodes.* Paloheimo used the electrodes supplied by Datex Instrumentarium for use with the Relaxograph, and took no special precautions to avoid movement-related artefacts. As the only changes in EEMG response reported here occurred during patient movement, it may be significant that different electrodes were used in the two studies. In a series of 100 consecutive patients, the Datex electrodes were associated with a failure of the EEMG to return to within ±10% of the control value in 40.5% of cases, while the Nikomed electrodes exhibited only an 8% failure rate; in addition, the Datex electrodes were associated with a 16% failure to achieve satisfactory calibration of the Relaxograph at the first attempt [author's unpublished observations].

*Nerve block.* Paloheimo studied six patients undergoing transurethral resection of prostate; subarachnoid block was obtained with isobaric 0.5% bupivacaine, and injection was made in the sitting position. The use of a different lumbar puncture technique, and hyperbaric instead of isobaric bupivacaine, is unlikely to have influenced the results, as a dense block adequate for surgery was obtained in both studies.

*EEMG monitoring.* Paloheimo used thenar or hypothenar EEMG in his volunteer group, and did not strap the hand. However, movement artefact occurs readily if the hand is not immobilized for EEMG monitoring (Datex application notes). Monitoring of flexor hallucis brevis EEMG was the same in both studies.

The lower motor neurone is the final common pathway for all neural traffic which converges on the motor end-plate [5]. Supramaximal stimulation of a peripheral nerve should excite all the lower motor neurones within that nerve, ensuring maximal response at the motor end-plate. This assumes that the nerve threshold for stimulation does not alter significantly after the stimulus current has been set. Any central motor mechanism which exerts its effect proximal to the site of nerve stimulation is, therefore, unlikely to modify the response of the motor end-plate to supramaximal external stimulation. Central modulation of plasma adrenaline concentration may modify neuromuscular performance [6] and nerve depolarization thresholds [7] under conditions of extreme stress, but these effects are small at physiological concentrations of adrenaline [6].

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# OESOPHAGEAL CONTRACTILITY DURING TOTAL I.V. ANAESTHESIA WITH AND WITHOUT GLYCOPYRRONIUM†

S. RAFTERY, G. ENEVER AND C. PRYS-ROBERTS

## SUMMARY

*Somatic movement and spontaneous and provoked oesophageal contractions were noted at time of incision in 51 patients receiving total i.v. anaesthesia with alfentanil and propofol. Probit analysis of the dose of propofol required to prevent spontaneous movement revealed an $ED_{50}$ (95% confidence limits) of 2.5 (1.8–2.9) mg $kg^{-1}$ $h^{-1}$ and $ED_{95}$ of 4.7 (4.0–7.5) mg $kg^{-1}$ $h^{-1}$. Corresponding venous blood concentrations gave an $EC_{50}$ of 1.2 (0.4–1.6) µg $ml^{-1}$ and an $EC_{95}$ of 4.0 (2.8–18.5) µg $ml^{-1}$. $ED_{50}$ of propofol for preventing spontaneous oesophageal contraction was 3.0 (1.9–3.6) mg $kg^{-1}$ $h^{-1}$. $ED_{95}$ was 6.9 (5.0–27.3) mg $kg^{-1}$ $h^{-1}$; $EC_{50}$ for oesophageal contractions was 1.7 (0.7–2.3) µg $ml^{-1}$ and $EC_{95}$ was 5.9 (3.7–70.6) µg $ml^{-1}$. Another group of 10 patients were given glycopyrronium 5 µg $kg^{-1}$ at induction; oesophageal contractility was significantly reduced in this group.*

### KEY WORDS

*Anaesthesia: depth. Gastrointestinal tract: oesophageal contractility. Pharmacology: glycopyrronium.*

In 1965, Eger, Saidman and Brandstater [1] introduced the concept of minimum alveolar concentration (MAC) of an inhaled anaesthetic as an index of potency and a means by which various agents could be compared. The original definition referred to the concentration required to prevent gross somatic movement in 50% of experimental animals. The concept was applied subsequently to MAC-BAR [2]—the concentration required to block adrenergic responses during anaesthesia. However, the MAC of an agent is only one point, the $EC_{50}$, on a concentration–response curve. It gives no indication of the slope of the concentration–response curve, and the $EC_{95}$ is a more relevant index in clinical practice [3, 4].

Similar considerations apply to i.v. agents, for which the Minimum Infusion Rate (MIR) corresponds to $ED_{50}$, and the corresponding plasma concentrations $EC_{50}$ and $EC_{95}$ may be determined from a concentration–response curve, the former being analogous to MAC.

Defining adequate anaesthesia in terms of the presence or absence of somatic movement is limited in any clinical setting in which neuromuscular blocking drugs are used. These suppress many signs of inadequate anaesthesia, but have no effect on consciousness. However, if the dose–response curve for a visceral reflex is shown to be close and parallel to that for gross somatic movement, it may be possible to monitor such visceral activity in paralysed patients and predict the likelihood of movement in an individual patient as though he were not paralysed.

Lower oesophageal contractility (LOC) [5] has been suggested as providing such an index of adequacy of anaesthesia. The lower oesophagus contains smooth muscle, and therefore should not be affected by the use of non-depolarizing myo-

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TABLE I. *Propofol infusion schemes in the six groups*

| Group | Loading dose ($mg\ kg^{-1}$) | Infusion No. 1 ($mg\ kg^{-1}\ h^{-1}$) | Infusion No. 2 ($mg\ kg^{-1}\ h^{-1}$) | Infusion No. 3 ($mg\ kg^{-1}\ h^{-1}$) |
|---|---|---|---|---|
| A | 1 | 10 | 8 | 6 |
| B | 0.75 | 7.5 | 6 | 4.5 |
| C | 0.6 | 6 | 4.8 | 3.6 |
| D, G | 0.5 | 5 | 4 | 3 |
| E | 0.4 | 4 | 3.2 | 2.4 |

neural blockers. Many researchers have attempted to correlate quantitative measures of oesophageal activity with evidence of inadequate anaesthesia, such as autonomic responses [6–10], movement [10–14], evoked potentials [15] or subsequent recall of intraoperative events [9, 14]. LOC is known to be affected by increasing doses of anaesthetic [7, 16] and type of surgical stimulus [7, 9, 17]. Dose–response curves for oesophageal visceral motor activity have not been determined.

Oesophageal smooth muscle is innervated by the vagus nerve and contains muscarinic receptors. These are affected by muscarinic antagonists such as atropine [18]. As these drugs are used frequently during anaesthesia it is important to determine if they may influence the reliability of oesophageal contractility monitoring.

We have determined the dose–response characteristics for oesophageal visceral motor responses and somatic motor responses in patients undergoing body surface surgery under total i.v. anaesthesia, and we have tested the hypothesis that glycopyrronium may alter oesophageal contractility.

## PATIENTS AND METHODS

We studied 61 healthy patients aged 40–65 yr, presenting for inguinal body surface surgery under general anaesthesia. The project was approved by the Ethics Committee of the Bristol and Weston Health Authority, and informed consent was obtained from each patient. Fifty-one patients were allocated randomly to one of five groups (A–E), each to receive differing infusions of propofol, and 10 were allocated to group G, to receive glycopyrronium before induction of anaesthesia and subsequent treatment as for group D (table I) [19–21].

The patients were premedicated with temazepam 20–30 mg 2 h before anaesthesia, which was induced with a loading dose of alfentanil 50 $\mu g\ kg^{-1}$ followed immediately by the initial loading dose of propofol (table I). A maintenance infusion of alfentanil 50 $\mu g\ kg^{-1}\ h^{-1}$ was started, and the appropriate first stage (infusion No. 1) of the three-stage propofol infusion was started. This was continued for 10 min, when the rate was reduced to that appropriate for infusion No. 2, and after a further 10 min the rate of infusion No. 3 was continued for the duration of surgery. Both infusions were delivered by calibrated Vickers IP4 syringe drivers.

Patients' lungs were inflated with 100% oxygen, and when the patient no longer responded to command, suxamethonium 1 $mg\ kg^{-1}$ was given to facilitate tracheal intubation and passage of an oesophageal probe which was connected to a Lectron 302 oesophageal contractility monitor (Antec Systems Ltd) [22]. The probe was passed to 35 cm below the teeth, and its position was confirmed by hearing breath and heart sounds through the integral stethoscope. The Lectron 302 was set up to monitor spontaneous oesophageal contractions, and every 90 s a 5-cm provocation balloon was inflated and the oesophageal pressure response to this was measured. A threshold of 15 cm $H_2O$ was set to eliminate artefacts resulting from transmitted pressures induced by artificial ventilation.

After intubation of the trachea, artificial ventilation was continued using an Oxford Penlon 400 ventilator with oxygen and entrained air ($FI_{O_2} = 0.3$), to produce a $PE'_{CO_2}$ of 4.8–5.2 kPa, measured by a Datex Multicap capnometer. Return of neuromuscular function was confirmed using a peripheral nerve stimulator before commencement of surgery.

At initial incision, the patient's motor response was noted as either movement or no movement. Presence of spontaneous and provoked oesophageal contractions was noted. A peripheral venous blood sample of 5 ml was taken for measurement of whole blood concentration of propofol by high pressure liquid chromatography [23]. If the patient moved at any time following

TABLE II. *Patient characteristics (mean (range))*

| Group | *n* | Age (yr) | Weight (kg) | Sex (M/F) |
|---|---|---|---|---|
| A | 11 | 51.2 (44–63) | 79.4 (64–95) | 9/2 |
| B | 10 | 55.4 (47–61) | 77.6 (58–105) | 9/1 |
| C | 10 | 54.1 (43–64) | 68.0 (53–83) | 5/5 |
| D | 10 | 52.9 (42–63) | 71.1 (52–88) | 6/4 |
| E | 10 | 56.8 (44–64) | 73.9 (54–92) | 9/1 |
| G | 10 | 54.5 (43–64) | 73.8 (56–106) | 10/0 |

TABLE III. *Mean time of groin incision after induction of anaesthesia, incidence of somatic and oesophageal responses, and whole blood concentration of propofol (mean* (SD)). *Patients in group G were given glycopyrronium 5 µg kg$^{-1}$, but otherwise were treated in the same way as those in group D. No significant difference between groups in time of incision.* **P = *0.0032 compared with group D* (t *test*)

| Group | *n* | Time (min) | Movement (No.) | SLOC (No ) | PLOC (No.) | Propofol concn (µg ml$^{-1}$) |
|---|---|---|---|---|---|---|
| A | 11 | 16.5 | 1 | 1 | 1 | 4.6 (1.4) |
| B | 10 | 17.1 | 0 | 1 | 2 | 2.7 (0.7) |
| C | 10 | 20.0 | 1 | 5 | 5 | 2.7 (0.5) |
| D | 10 | 15.4 | 2 | 5 | 2 | 1.8 (0.5) |
| E | 10 | 15.8 | 7 | 6 | 4 | 1.8 (0.9) |
| G | 10 | 15.4 | 5 | 0 | 1 | 1.2 (0.3)** |

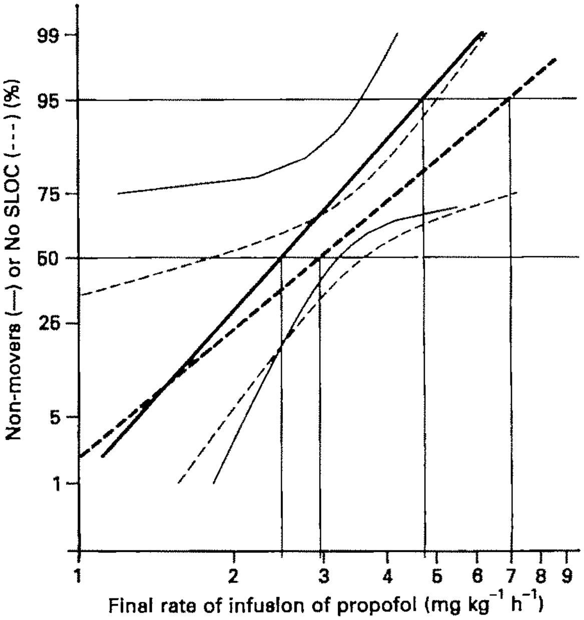

FIG. 1. Log dose–probit response curves and 95 % confidence intervals for the number of patients who did not move (——) and those who had no spontaneous oesophageal contraction (---) as functions of the final infusion rate of propofol. The equations are: Probit (no movement) = 5.88 × $\log_{10}$(final infusion rate) − 2.32; Probit (no SLOC) = 4.47 × $\log_{10}$(final infusion rate) − 2.10.

incision, further increments of propofol 20 mg were given and recorded. Subsequent anaesthesia was maintained with the propofol infusion at 6 mg kg$^{-1}$ h$^{-1}$. Patients were interviewed after operation to elicit recall of events related to anaesthesia.

When the dose–response variables for oesophageal motility had been calculated, another 10 patients (group G) were given glycopyrronium 5 µg kg$^{-1}$ immediately before induction of anaesthesia. They received the same loading dose and infusion regimen as those in group D, which was equivalent to the calculated $ED_{50}$ for spontaneous oesophageal contractions, and were examined in the same way as the other patients.

Analysis of data was carried out using SAS software (SAS for PC, version 6.03, SAS Institute, Cary, NC, U.S.A.). Demographic data were analysed for statistical significance using one-way analysis of variance. Probit analysis of the ratio of movers to non-movers and the ratio of those patients with spontaneous or provoked

TABLE IV. *Calculated final infusion rates and whole blood concentration of propofol required to abolish responses to groin incision (value (95 % confidence limits)). Confidence limits could not be calculated for the PLOC data*

| Response | $ED_{50}$ (mg kg$^{-1}$ h$^{-1}$) | $ED_{95}$ (mg kg$^{-1}$ h$^{-1}$) | $EC_{50}$ (µg ml$^{-1}$) | $EC_{95}$ (µg ml$^{-1}$) |
|---|---|---|---|---|
| Movement | 2.5<br>(1.8–2.9) | 4.7<br>(4.0–7.5) | 1.2<br>(0.4–1.6) | 4.0<br>(2.8–18.5) |
| SLOC | 3.0<br>(1.9–3.6) | 6.9<br>(5.0–27.3) | 1.7<br>(0.7–2.3) | 5.9<br>(3.7–70.6) |
| PLOC | 1.9 | 11.6 | 1.1 | 7.8 |

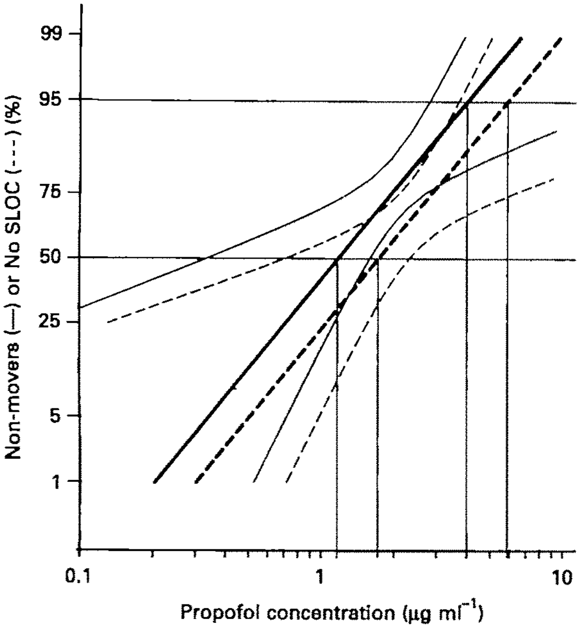

FIG. 2. Log concentration–probit response curves and 95 % confidence intervals for non-movers (——) and patients with no spontaneous oesophageal contraction (---) as functions of the measured propofol concentration. The equations are: Probit (no movement) = 3.08 × $\log_{10}$ (concentration) − 0.20; Probit (no SLOC) = 3.08 × $\log_{10}$ (concentration) − 0.72.

oesophageal contractions to those without was used to determine the dose–response curves of propofol for somatic movement and for oesophageal contractions [24]. Linear regression analysis was used to assess the correlation between blood concentration of propofol at incision and rate of infusion of propofol. In order to improve the confidence of the parameter estimates for movement and for blood concentration of propofol, the data from Richards [21], using an identical anaesthetic technique, were incorporated into these analyses. The proportions of those patients with and without oesophageal contractions in the glycopyrronium group and group D were tested with Fisher's exact test.

## RESULTS

Patients in each group were similar in age, weight and sex distribution (table II). No patient recalled any event during anaesthesia.

The time of incision after induction of anaesthesia, numbers of patients who moved in response to the initial surgical incision and those who had spontaneous (SLOC) or provoked (PLOC) lower oesophageal contractions, and the mean whole blood concentration of propofol are displayed in table III.

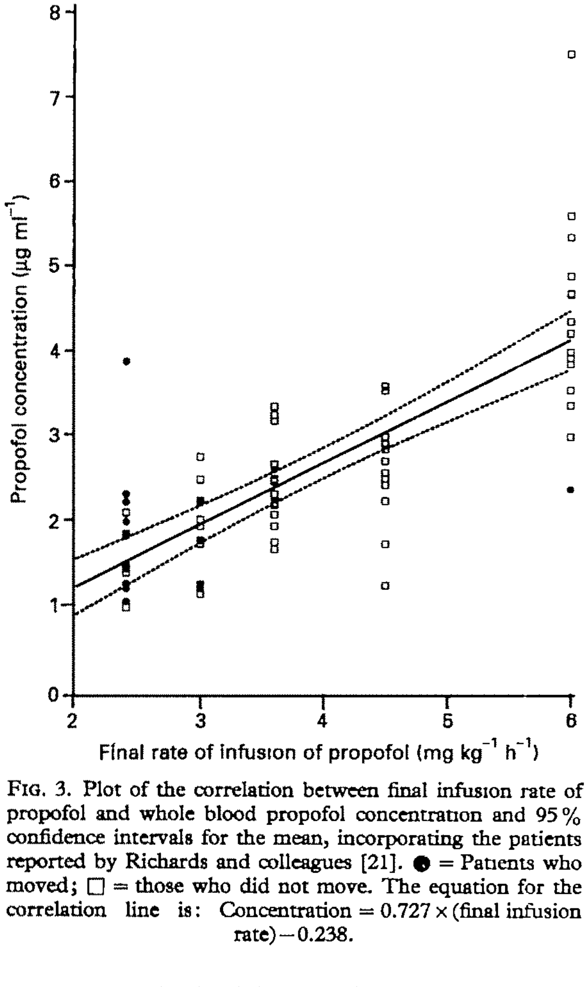

FIG. 3. Plot of the correlation between final infusion rate of propofol and whole blood propofol concentration and 95 % confidence intervals for the mean, incorporating the patients reported by Richards and colleagues [21]. ● = Patients who moved; □ = those who did not move. The equation for the correlation line is: Concentration = 0.727 × (final infusion rate) − 0.238.

Calculated values and 95 % confidence intervals for $ED_{50}$, $ED_{95}$, $EC_{50}$ and $EC_{95}$ of propofol for somatic movement and for oesophageal contractions are displayed in table IV.

Figure 1 shows the log dose–probit response curve for somatic movement and spontaneous oesophageal contractions as functions of the final infusion rate of propofol. Figure 2 shows the same responses as functions of the measured propofol concentration. The curves for somatic movement and for SLOC are close and parallel in both of these. Figure 3 displays the correlation between final infusion rate of propofol and whole blood concentration of propofol.

### *Effect of glycopyrronium*

The 10 patients given glycopyrronium (group G) were not significantly different in age or weight from those in any other group (table II). None of the patients given glycopyrronium displayed spontaneous oesophageal contractility, despite an expected incidence of 50% as found in group D ($P = 0.033$). The whole blood concentration of propofol was less in those patients who received glycopyrronium (table III) ($P = 0.0032$).

## DISCUSSION

Guedel's description of the signs associated with the stages of anaesthesia provided an index of "depth" of anaesthesia. Many of these signs, such as ventilatory frequency and depth and muscle tone, depend upon neuromuscular function. With the introduction of neuromuscular blocking drugs into anaesthetic practice, it was possible to achieve good surgical conditions with low concentrations of anaesthetic vapour, avoiding problems of cardiac and respiratory depression. This also led to the loss of the traditional signs of inadequate anaesthesia, and an increased likelihood of awareness because of too small a concentration of anaesthetic. Since then, anaesthetists have learned to rely on autonomic signs of inadequate anaesthesia such as heart rate, arterial pressure, sweating and lachrymation. However, all these signs can be influenced by other factors and are not accurate indices of adequate anaesthesia. Techniques that may be useful in monitoring anaesthesia include frontalis muscle EMG, raw and processed EEG, and cortical evoked responses.

Evans [5] suggested that oesophageal contractility may be useful as an index of adequacy of anaesthesia during surgery. Many studies since have attempted to relate oesophageal contractility to autonomic responses during surgery [6–10], movement of an isolated limb [10, 13, 14] or auditory evoked responses [15]. Attempts have been made to quantify oesophageal responses, either as the rate of spontaneous contractions or the amplitude of provoked contractions, in order to provide a threshold level of oesophageal activity above which awareness may be present [10]. Another variable, the oesophageal contractility index (OCI) [22], has been postulated to summarize these two responses. However, there is great variation between patients, different surgical stimuli and different anaesthetic techniques.

As consciousness resides in the brain, rather than in the oesophagus, it is inappropriate to regard oesophageal contractility as a monitor of awareness. However, if it is assumed that a patient with normal neuromuscular function who does not move when a surgical incision is made is unconscious, and if it can be shown that visceral motor responses such as oesophageal contractility have a dose–response curve similar to that for somatic motor responses, it may be deduced that absence of visceral activity is likely to be associated with unconsciousness.

In this study we made no attempt to quantify oesophageal contractions, but merely noted them as either present or absent. By analogy with studies of MAC for inhaled agents, we examined the patient's response to a single defined stimulus—incision of the groin. Using a standard anaesthetic technique, we have shown that the dose–response curves for somatic movement and spontaneous oesophageal contraction as functions of blood concentration of propofol are parallel and close, with the curve for spontaneous oesophageal contraction lying to the right of that for movement. This suggests that quantal response of spontaneous oesophageal contraction, rather than amplitude of contraction considered as a continuous variable, is related closely to the probability of somatic movement in unparalysed patients.

Previous work has shown a wide variation in the amplitude and frequency of oesophageal contraction. Our results confirm this wide variation, as shown by the 95% confidence intervals for infusion rates and propofol concentrations. When these data are plotted on a logarithmic axis (figs 1, 2) it can be seen that a large element of the variation is attributable to the nature of a logarithmically-mapped variable.

The use of glycopyrronium has been recommended for preventing hypotension and bradycardia that can occur with this technique of total i.v. anaesthesia [25]. It has been shown that anticholinergic agents may decrease amplitude of oesophageal peristaltic contraction in conscious subjects [18]; we therefore tested the hypothesis that, under the condition of anaesthesia, such effects may limit the applicability of this technique. The whole blood concentration of propofol was smaller in our patients who were given glycopyrronium—possibly because of changes in cardiac output or liver blood flow which may have increased the metabolism of the drug. Despite having a significantly smaller concentration of propofol, we found that those patients given glycopyrronium had a reduced incidence of spontaneous oesophageal contraction. We recommend, therefore, that anticholinergic medication should be avoided if spontaneous oesophageal contractility is to be monitored as an index of adequate anaesthesia.

The dose–response curve for provoked oesophageal contractions was rather more shallow than that for spontaneous contractions. This is in accord with previous findings of provoked contractions in brain-dead subjects [26]. We suggest that using provoked oesophageal contractions or the oesophageal contractility index is inappropriate for assessing adequacy of anaesthesia.

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*British Journal of Anaesthesia* 1991; **66**: 572–579

# ARTERIAL WASHIN OF HALOTHANE AND ISOFLURANE IN YOUNG AND ELDERLY ADULT PATIENTS

## R. C. DWYER, J. P. H. FEE, P. J. HOWARD AND R. S. J. CLARKE

### SUMMARY

*We have studied the effect of age on washin of isoflurane and halothane by comparing end-tidal (P*E′*) and arterial (P*a*) partial pressures of the agents in young (18–32 yr) and elderly (63–82 yr) healthy patients for 20 min after introduction of the agents, before surgery. P*E′ *was measured by infra-red analysis and P*a *by gas chromatography. Washin of isoflurane occurred at the same rate in the young and elderly, with no significant difference between young and elderly in P*E′ *or P*a *as proportions of the inspired partial pressure (P*I*). After 20 min of isoflurane administration, mean P*a*/P*I *in the young was 0.57 (95% confidence limit (CL) 0.53–0.62) and 0.55 in the elderly (95% CL 0.51–0.59). Washin of halothane was slower in the elderly than in the young, with P*a*/P*I *significantly less in the elderly from 10 min after introduction of halothane. The difference between age groups, however, was small: mean P*a*/P*I *after 20 min of halothane administration 0.45 (95% CL 0.41–0.49) in the young and 0.38 (95% CL 0.35–0.41) in the elderly. Washin of isoflurane was significantly faster than that of halothane in both young and elderly subjects. For isoflurane, the P*E′*–P*a *gradient was small relative to P*a *and did not differ significantly between young and elderly. For halothane, P*E′*–P*a *in the young did not differ significantly from that for isoflurane. In the elderly, P*E′*–P*a *for halothane was significantly greater than in the young and than P*E′*–P*a *for isoflurane.*

***KEY WORDS***

*Anaesthetics, volatile. halothane, Isoflurane. Pharmacokinetics. uptake. Age factors*

Administration of a volatile anaesthetic agent is facilitated by ability to predict the rate of washin (increase of partial pressures) of the agent following its introduction. The factors governing the rate of washin include alveolar ventilation, pulmonary function, cardiac output, the proportion of body mass composed of vessel rich, muscle and fat groups of tissues, and the blood/gas and tissue/blood partition coefficients of the agent [1]. The normal physiological process of ageing changes many of these: ventilation–perfusion ($\dot{V}/\dot{Q}$) inequality in the lungs increases, while diffusing capacity decreases [2]; basal metabolic rate decreases, leading to decreased production of carbon dioxide and decreased minute ventilation [3]; tissue/blood partition coefficients increase [4]; and fat increases as a proportion of body mass [5]. These changes tend to decrease the rate of washin of volatile agents. Other ageing-induced physiological changes, however, tend to increase the rate of washin of volatile agents: the blood/gas partition coefficients of volatile agents decrease [6] and cardiovascular depression by volatile agents is greater in the elderly [7–9].

Previously, we have compared washin of volatile agents in the young and elderly by measuring end-tidal concentrations of isoflurane and halothane in young and elderly normocapnic patients [10]. End-tidal isoflurane concentrations increased more slowly in the elderly; end-tidal halothane concentrations increased at the same rate in both age groups. However, two factors may modify interpretation of the results of this study. First, the elderly have a greater gradient between end-tidal ($P\text{E}'_{\text{CO}_2}$) and arterial ($P\text{a}_{\text{CO}_2}$) partial pressures of carbon dioxide [11] and ventilating both groups to the same $P\text{E}'_{\text{CO}_2}$ may have caused relative

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underventilation of the elderly. This could explain slower washin of isoflurane in the elderly. Second, ageing increases ventilation–perfusion ($\dot{V}/\dot{Q}$) inequality [2]. End-tidal volatile agent partial pressures overestimate arterial partial pressures in the presence of $\dot{V}/\dot{Q}$ inequality [12] and in the elderly may not accurately represent arterial or cerebral partial pressures. Arterial partial pressures, however, reflect cerebral partial pressures in the young [13, 14] and presumably in the elderly also.

To clarify the effects of ageing on washin of isoflurane and halothane, we measured arterial partial pressures of the agents in young and elderly patients undergoing ventilation to the same $Pa_{CO_2}$.

## PATIENTS AND METHODS

Forty-one healthy (ASA grade I or II) patients were studied before elective orthopaedic surgery. All gave informed consent and the study was approved by the University Medical Research Ethics Committee. Patients with clinical evidence of respiratory or cardiovascular disease, and patients who were hypertensive (defined as a diastolic arterial pressure greater than 90 mm Hg) or obese (defined as a body weight greater than 120 % of that predicted for age and height) were excluded. Twenty-one were young (18–32 yr) and 20 were elderly (63–82 yr); 20 subjects received isoflurane (10 young and 10 elderly), and the remainder received halothane. The two agents were not studied concurrently; all subjects who received isoflurane were studied before the subjects who received halothane. None of the subjects receiving halothane had been exposed recently to the agent.

Diazepam 0.15 mg kg$^{-1}$ was administered orally 1 h before anaesthesia. After insertion of a 22-gauge radial artery cannula, anaesthesia was induced with a dose of thiopentone sufficient to obtund the eyelash reflex and alfentanil 15 μg kg$^{-1}$; neuromuscular block was provided by pancuronium 0.1 mg kg$^{-1}$. The lungs were ventilated manually with oxygen and the trachea was intubated with a tracheal tube which incorporated a gas sampling lumen (Portex). Intermittent positive pressure ventilation with oxygen was continued using a non-rebreathing system. Halothane or isoflurane was introduced in a concentration of 1 % (by vaporizer setting). Ventilation was adjusted to maintain $P\text{E}'_{CO_2}$ at 4.8 kPa in the young or 4.5 kPa in the elderly, as measured by infra-red carbon dioxide analysis (Hewlett–Packard 47210A, calibrated using the calibration cell supplied). These values for $P\text{E}'_{CO_2}$ were chosen as likely to result in a $Pa_{CO_2}$ of 5.3 kPa.

The ECG, $P\text{E}'_{CO_2}$ and nasopharyngeal temperature were monitored continuously and arterial pressure was measured by automated oscillotonometer. Mean arterial pressure (MAP) was maintained greater than 60 mm Hg in all patients, if necessary by elevation of the legs. Two elderly patients receiving isoflurane and four receiving halothane required infusion of up to 300 ml of Dextran 70 to maintain MAP greater than this value. $Pa_{CO_2}$ was measured 10 and 20 min after introduction of the volatile agent using an automated blood-gas analyser (IL 1302), calibrated at 1-h intervals using standard carbon dioxide mixtures.

Gas from the distal trachea was sampled continuously via the gas sampling lumen of the tracheal tube and the end-tidal partial pressure of volatile agent was measured by infra-red analysis (Datex "Normac"). This monitor has a rapid response time and is accurate at concentrations used clinically [15]. Calibration was performed before each case using a known concentration of difluorochloromethane ($CHClF_2$). The analog output of the vapour analyser was attached to a microcomputer (BBC "B") to calculate the inspired and end-tidal partial pressures of volatile agent [16].

The accuracy of the infra-red vapour analyser was tested by comparing gas concentrations in the anaesthetic circuit measured by the analyser with those in samples drawn from the circuit and measured by gas chromatography. The infra-red analyser underestimated isoflurane and halothane partial pressures relative to gas chromatography. For isoflurane, the mean error was 6 % with 95 % "limits of agreement" (LA) for differences between the two methods of measurement (i.e. two standard deviations, as described by Bland and Altman [17]) of ±8 %. For halothane the mean error was 1 % with 95 % LA of ±20 %. The data have not been corrected for these errors.

Samples of arterial blood were obtained for measurement of isoflurane or halothane partial pressures at 2, 5, 10, 15 and 20 min after introduction of the agent. After clearing the deadspace (0.7 ml) of the arterial cannula by discarding the initial 3 ml, 5–6 ml of arterial blood was obtained from the three-way tap on the cannula. Samples were drawn anaerobically into gas-tight, glass 10-ml syringes (Hamilton 1010 TLL). The syringes had a Teflon-coated plunger and were sealed with a Teflon-coated gas-tight stopcock (Mininert) until analysis. The deadspace of the syringe (0.2 ml) had been filled beforehand with heparin 1000 iu $ml^{-1}$. Because of the low solubility of volatile agent in crystalloid solutions, the heparin solution was ignored in subsequent calculations. A sample of inspiratory gas was taken from the anaesthetic circuit 12 min after introduction of volatile agent.

Halothane and isoflurane partial pressures in blood and inspired gas were measured using a gas chromatograph (GC) (Perkin Elmer F33) equipped with a gas sampling valve (sampling loop 0.5 ml) and a flame ionization detector. The column was 60 cm long and 3 mm in diameter, made of borosilicate glass and packed with a polymer of styrene and ethylvinyl-benzene (Poropak Q). The carrier gas was oxygen-free nitrogen and the detector was supplied by hydrogen and air. Column temperature was 175 °C and detector temperature 225 °C. The retention time for isoflurane was 81 s, for halothane 119 s.

The GC was calibrated using four standards made by injecting measured amounts of liquid isoflurane from a microsyringe into gas-tight flasks of known volume. The volatile agent partial pressure in each standard was calculated and the chromatograph calibrated by plotting the peak heights of the standards against their known isoflurane or halothane partial pressures. The GC response to both agents was linear over a wide range of partial pressures. The coefficient of variation for measurement of volatile agent partial pressures in gas samples was 1.5 % for isoflurane and less than 1 % for halothane.

Analysis of blood samples for isoflurane or halothane partial pressure commenced within 1 h of drawing the samples, using the method described by Fink and Morikawa [18]. Excess blood was ejected from each syringe until exactly 5 ml remained in the syringe. Five millilitre of humidified air was drawn into the syringe and equilibrated with the blood in the syringe for 30 min on a rotating disc, at room temperature. Longer periods of equilibration produced no increase in partial pressures of volatile agent in the headspace gas above the blood. The headspace gas was injected into the GC and the volatile agent partial pressure in the gas (and thus blood) measured ($P_1$). The process was repeated: all air was removed from the syringe and a fresh 5 ml of humidified air drawn in. Equilibration of volatile agent partial pressures between blood and gas phases was again carried out for 30 min and the volatile agent partial pressure in the headspace gas ($P_2$) measured. The product of $P_1$ and the ratio $P_1$:$P_2$ gave the partial pressure of halothane or isoflurane in the original blood sample at room temperature. This was converted to the partial pressure at body temperature by multiplying it by the ratio of saturated vapour pressure (SVP) at body temperature to the SVP at room temperature, in accordance with the theory given by Fink and Morikawa [18] (which gives results consistent with experimental data on the changes in blood solubility with temperature [19]). The SVP at each temperature was calculated using the Antoine equation as described for isoflurane [20] and halothane [21]. Blood partial pressures of isoflurane were expressed as % of 1 standard atmosphere (% Atm).

The coefficient of variation for estimation of blood partial pressure was calculated on 10 samples drawn from a subject at a stable end-tidal concentration of each agent, and was found to be 2.4% for isoflurane, 5.6% for halothane.

The accuracy of measurement of blood partial pressures at room temperature was tested in blood samples of known blood partial pressure, prepared by equilibrating blood samples from a single volunteer with gas containing the volatile agent in a range of concentrations. All analyses were performed at room temperature. After equilibration so that partial pressures in the blood ($Pb$) and headspace gas were equal, the partial pressure of volatile agent in the headspace gas ($Pb$) was measured. Headspace gas was removed, the blood was equilibrated with air on two further occasions and partial pressures of volatile agent in the headspace gas ($P_1$ and $P_2$) measured after each equilibration. The partial pressure of volatile agent in the original specimen was calculated as $P_1(P_1/P_2)$ and compared with $Pb$, which had been measured directly. For isoflurane ($n = 22$), the calculated value for $Pb$ underestimated the measured value by a mean 4% (95% LA ±7%), and for halothane ($n = 10$) by a mean 5% (95% LA ±10%). The data have not been corrected for these errors.

The blood/gas partition coefficient of each blood sample at 37 °C was calculated using the ratio $P_1$:$P_2$ according to the theory of Fink and Morikawa [18].

TABLE I. *Sex distribution, number of smokers, mean (range) ages and mean* (SD) *weights of the young and elderly patients*

| | Isoflurane | | Halothane | |
|---|---|---|---|---|
| | Young | Elderly | Young | Elderly |
| *n* | 10 | 10 | 11 | 10 |
| Sex (M/F) | 5/5 | 4/6 | 6/5 | 4/6 |
| Age (yr) | 28 (22–32) | 69 (63–81) | 26 (21–30) | 70 (63–82) |
| Weight (kg) | 68 (10.0) | 72 (10.6) | 66 (12.7) | 67 (13.2) |
| Smokers (No.) | 5 | 2 | 4 | 2 |

TABLE II. *Mean* (SD) *mean arterial pressure (MAP), heart rate (HR) and* $Pa_{CO_2}$ *(corrected for body temperature), in young and elderly patients.* *P < 0.05 *for difference between young and elderly*

| | Isoflurane | | Halothane | |
|---|---|---|---|---|
| Time (min) | Young | Elderly | Young | Elderly |
| MAP (mm Hg) | | | | |
| 0 | 104 (16) | 96 (21) | 106 (20) | 106 (16) |
| 2 | 93 (13) | 87 (12) | 96 (18) | 95 (13) |
| 5 | 87 (7) | 83 (14) | 91 (17) | 87 (19) |
| 10 | 88 (6) | 89 (17) | 87 (15) | 83 (20) |
| 15 | 89 (12) | 89 (14) | 85 (15) | 82 (11) |
| 20 | 88 (11) | 90 (12) | 84 (13) | 78 (8) |
| HR (beat min$^{-1}$) | | | | |
| 0 | 94 (20) | 80 (17) | 105 (20) | 83 (12)* |
| 5 | 91 (14) | 78 (15) | 104 (17) | 80 (11)* |
| 10 | 89 (17) | 75 (14) | 101 (16) | 81 (14)* |
| 15 | 88 (22) | 74 (14) | 97 (15) | 77 (11)* |
| 20 | 89 (22) | 73 (14) | 94 (13) | 74 (11)* |
| $Pa_{CO_2}$ (kPa) | | | | |
| 10 | 5.3 (0.3) | 5.2 (0.3) | 4.9 (0.4) | 4.8 (0.5) |
| 20 | 5.2 (0.3) | 5.2 (0.3) | 4.8 (0.4) | 4.7 (0.5) |

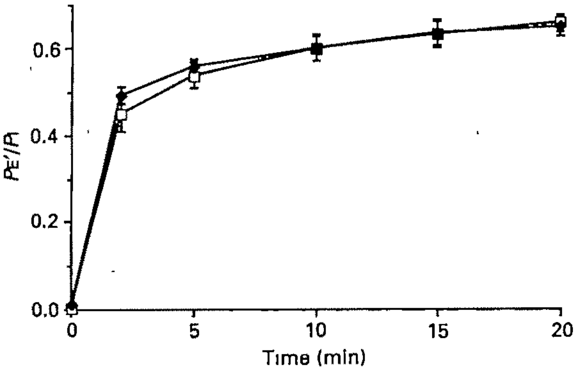

FIG. 1. End-tidal isoflurane partial pressures (*P*E′), as a proportion of the inspired (*P*I) (means, 95 % confidence limits) in young (□) and elderly (◆) patients.

End-tidal (*P*E′) and arterial (*P*a) partial pressures were expressed as proportions of the inspired partial pressure (*P*I) before statistical analysis to correct for differences in *P*I between groups. Statistical analysis was by two-factor (age group or agent, and time) repeated measures analysis of variance and unpaired *t* test, as appropriate; $P < 0.05$ was considered statistically significant.

## RESULTS

Patient characteristics are shown in table I. For isoflurane, heart rate and arterial pressure did not differ significantly between young and elderly (table II). For halothane, heart rates were less in the elderly than in the young, but there was no significant difference in mean arterial pressure. Body temperature did not differ between the groups. $Pa_{CO_2}$ did not differ significantly between young and elderly receiving either halothane or isoflurane, but was significantly less in subjects receiving halothane than in those given isoflurane (table II).

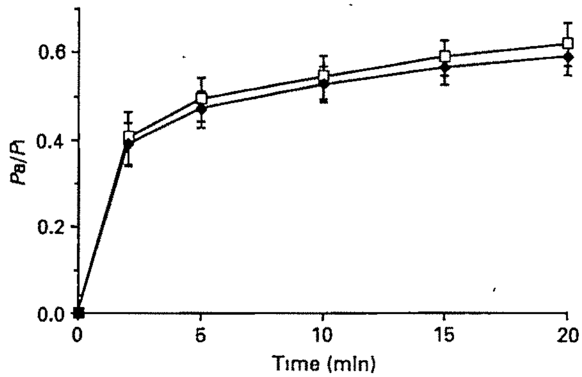

FIG. 2. Arterial isoflurane pressures ($P\text{a}$), as a proportion of the inspired ($P\text{I}$) (means, 95% confidence limits) in young (□) and elderly (◆) patients.

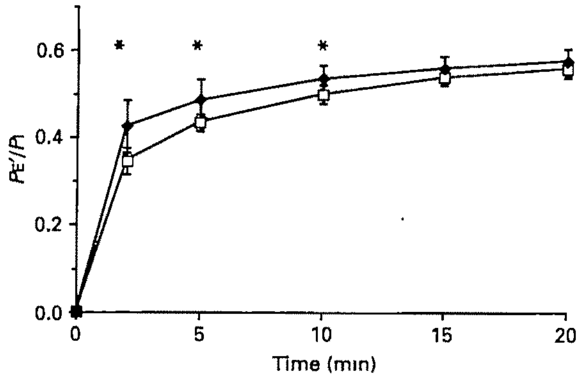

FIG. 3. End-tidal halothane pressures ($P\text{E}'$), as a proportion of the inspired ($P\text{I}$) (means, 95% confidence limits). $^*P < 0.05$ for difference between young (□) and elderly (◆).

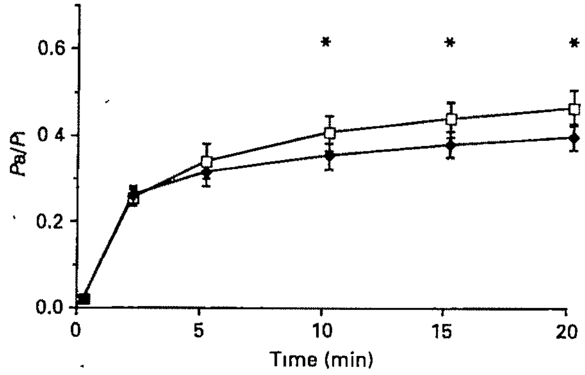

FIG. 4. Arterial halothane pressures ($P\text{a}$), as a proportion of the inspired ($P\text{I}$) (means, 95% confidence limits). $^*P < 0.05$ for difference between young (□) and elderly (◆).

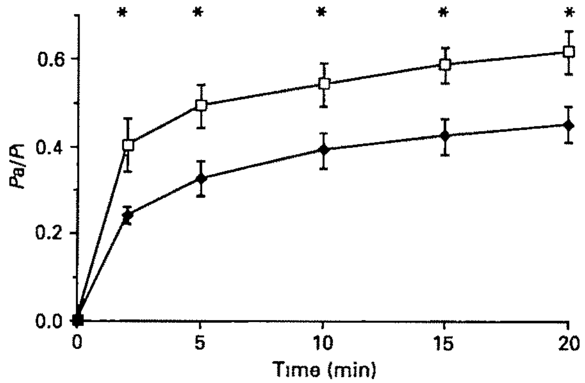

FIG. 5. Arterial halothane (◆) and isoflurane (□) pressures ($P\text{a}$), as a proportion of the inspired ($P\text{I}$), in young patients (means, 95% confidence limits). $^*P < 0.05$ for difference between isoflurane and halothane.

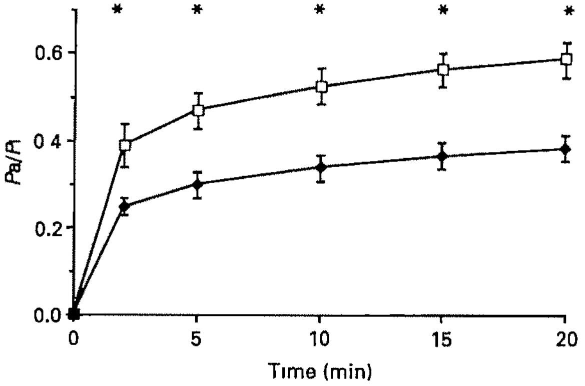

FIG. 6. Arterial halothane (◆) and isoflurane (□) pressures ($P\text{a}$), as a proportion of the inspired ($P\text{I}$), in elderly patients (means, 95% confidence limits). $^*P < 0.05$ for difference between isoflurane and halothane.

For isoflurane, $P\text{E}'/P\text{I}$ and $P\text{a}/P\text{I}$ were similar in young and elderly for 20 min following the introduction of isoflurane (figs 1, 2). Mean $P\text{I}$ of isoflurane (measured by GC) was 0.94 (SD 0.19)% Atm in the young and 0.95 (0.12)% Atm in the elderly.

For halothane, $P\text{E}'/P\text{I}$ was greater in the elderly for the first 10 min of administration; subsequently there was no difference between the age groups (fig. 3). $P\text{a}$ for halothane, however, increased more slowly in the elderly than in the young and $P\text{a}/P\text{I}$ values were significantly less in the elderly after 10 min of halothane administration (fig. 4). $P\text{I}$ for halothane (measured by GC) was 0.96 (0.19)% Atm in the elderly and 0.85 (0.16)% Atm in the young.

$P\text{a}/P\text{I}$ values were significantly greater for

TABLE III. *Arterial (Pa) and end-tidal ($P_{E'}$) partial pressures of isoflurane as fractions of the inspired partial pressure ($P_I$), and ($P_{E'}/P_I$)−($Pa/P_I$) differences in young and elderly patients (mean (95% confidence limits))*

| Time (min) | $P_{E'}/P_I$ | $Pa/P_I$ | $(P_{E'}/P_I)-(Pa/P_I)$ |
|---|---|---|---|
| Young | | | |
| 0 | | | |
| 2 | 0.45 (0.41–0.49) | 0.38 (0.32–0.43) | 0.07 (0.02–0.11) |
| 5 | 0.54 (0.51–0.57) | 0.46 (0.41–0.50) | 0.08 (0.04–0.12) |
| 10 | 0.60 (0.58–0.63) | 0.50 (0.45–0.55) | 0.10 (0.05–0.14) |
| 15 | 0.63 (0.61–0.66) | 0.54 (0.51–0.58) | 0.08 (0.05–0.12) |
| 20 | 0.66 (0.64–0.68) | 0.57 (0.53–0.62) | 0.09 (0.05–0.14) |
| Elderly | | | |
| 0 | | | |
| 2 | 0.49 (0.47–0.51) | 0.36 (0.32–0.41) | 0.13 (0.08–0.17) |
| 5 | 0.56 (0.54–0.58) | 0.44 (0.40–0.48) | 0.12 (0.08–0.15) |
| 10 | 0.60 (0.57–0.63) | 0.49 (0.45–0.53) | 0.11 (0.08–0.14) |
| 15 | 0.64 (0.61–0.66) | 0.53 (0.48–0.57) | 0.11 (0.07–0.15) |
| 20 | 0.65 (0.63–0.67) | 0.55 (0.51–0.59) | 0.10 (0.06–0.13) |

TABLE IV. *Arterial (Pa) and end-tidal ($P_{E'}$) partial pressures of halothane as fractions of the inspired partial pressure ($P_I$), and ($P_{E'}/P_I$)−($Pa/P_I$) differences in young and elderly patients (mean (95% confidence limits)). *$P < 0.05$ compared with value in young group*

| Time (min) | $P_{E'}/P_I$ | $Pa/P_I$ | $(P_{E'}/P_I)-(Pa/P_I)$ |
|---|---|---|---|
| Young | | | |
| 0 | | | |
| 2 | 0.34 (0.32–0.37) | 0.24 (0.22–0.26) | 0.11 (0.07–0.16) |
| 5 | 0.43 (0.41–0.45) | 0.33 (0.28–0.37) | 0.12 (0.07–0.17) |
| 10 | 0.50 (0.48–0.52) | 0.39 (0.35–0.43) | 0.12 (0.08–0.16) |
| 15 | 0.54 (0.52–0.56) | 0.42 (0.38–0.46) | 0.13 (0.10–0.17) |
| 20 | 0.56 (0.54–0.58) | 0.45 (0.41–0.49) | 0.12 (0.09–0.16) |
| Elderly | | | |
| 0 | | | |
| 2 | 0.42 (0.37–0.48) | 0.25 (0.23–0.26) | 0.18 (0.13–0.23)* |
| 5 | 0.48 (0.44–0.53) | 0.30 (0.27–0.33) | 0.20 (0.16–0.24)* |
| 10 | 0.53 (0.50–0.56) | 0.34 (0.31–0.37) | 0.20 (0.17–0.24)* |
| 15 | 0.56 (0.53–0.59) | 0.36 (0.34–0.39) | 0.20 (0.17–0.23)* |
| 20 | 0.58 (0.55–0.60) | 0.38 (0.35–0.41) | 0.20 (0.17–0.23)* |

isoflurane than halothane in both young (fig. 5) and elderly (fig. 6) subjects.

For isoflurane, the gradient between end-tidal and arterial partial pressures $(P_{E'}/P_I)-(Pa/P_I)$ did not differ significantly between the young and elderly (table III). For halothane, the $(P_{E'}/P_I)-(Pa/P_I)$ gradient was greater in the elderly than in the young (table IV). In young subjects the $(P_{E'}/P_I)-(Pa/P_I)$ gradient did not differ significantly between isoflurane and halothane, but in elderly subjects the gradient was significantly greater for halothane than for isoflurane.

The blood/gas partition coefficient for isoflurane was significantly less in the elderly (mean 1.31, 95% confidence limits (CL) 1.21–1.41) than in the young (mean 1.48, 95% CL 1.36–1.59) ($P < 0.05$). The mean blood/gas partition coefficient for halothane was 2.82 (95% CL 2.56–3.07) in the elderly and 3.03 (95% CL 2.74–3.32) in the young.

## DISCUSSION

Washin of isoflurane occurred at the same rate in healthy elderly patients as in the young, despite the physiological changes associated with ageing. With both age groups at the same $Pa_{CO_2}$, $P_{E'}$ and $Pa$ of isoflurane did not differ between young and elderly following introduction of the agent (figs 1, 2). Washin of halothane, however, occurred more slowly in the elderly, with $Pa$ of halothane significantly less in the elderly than in the young (fig. 4). The difference between the age groups was small, and unlikely to be of major clinical significance (especially as it is partly compensated for by the lower minimum alveolar concentration (MAC) for halothane in the elderly [22]). Our study continued for only 20 min after introduction of the agents, and it is uncertain if $Pa$ of halothane remained smaller in the elderly over a longer period.

Thus the physiological changes of ageing altered the washin of halothane but not of isoflurane. In the elderly, tissue/blood partition coefficients increase [4], fat increases as a proportion of body mass [5] and minute ventilation decreases because of reduced metabolic rate [3]. These changes have a proportionately greater effect in slowing the washin of the more soluble agent, halothane [1], and this may explain why ageing slowed the washin of halothane but not that of isoflurane.

Washin of isoflurane occurred more rapidly than washin of halothane in both young and elderly patients (figs 5, 6), despite slight relative underventilation in the isoflurane group (table II). This is consistent with the lower blood/gas partition coefficient of isoflurane and with results from previous studies [10, 23, 24]. The difference between the rates of uptake of the two agents is of sufficient magnitude to be clinically significant.

Our values for $Pa/PI$ and $PE'/PI$ during washin of isoflurane were slightly less (10%) and slightly greater, respectively, than those found by Cromwell and colleagues in awake volunteers spontaneously breathing subanaesthetic concentrations of isoflurane [23]. The differing results may be explained by increased $\dot{V}/\dot{Q}$ inequality and intrapulmonary shunting in our patients because of anaesthesia and positive pressure ventilation [25]; these pulmonary changes increase $PE'$ and decrease $Pa$ [12]. Similarly, our values for $Pa/PI$ and $PE'/PI$ for halothane were, respectively, less and greater than those found by Munson and colleagues in conscious young volunteers spontaneously breathing subanaesthetic concentrations of halothane [24]. $PE'/PI$ values found by Torri and co-workers in anaesthetized young patients were similar to ours [26].

$PE'/PI$ values for isoflurane and halothane in the current study are consistent with those in our earlier study when both young and elderly patients had the same $PE'_{CO_2}$ (4.7 kPa) [10]. In the previous study, $PE'/PI$ values for isoflurane were smaller in the elderly than in the young, and for halothane there was no difference between age groups. In the current study, with the elderly at a smaller $PE'_{CO_2}$ than the young, $PE'/PI$ values for isoflurane did not differ between young and elderly (fig. 1) and $PE'/PI$ values for halothane were, for a period, greater in the elderly. The effect of the slight increase in alveolar ventilation on $PE'/PI$ in the elderly relative to the young demonstrates the importance of alveolar ventilation in determining the rate of washin of volatile agents.

For isoflurane, $PE'-Pa$ gradients were small relative to $Pa$, and $PE'$ was a useful guide to $Pa$ in both young and elderly (table III). For halothane, $PE'-Pa$ in the young did not differ significantly from that found for isoflurane, but $PE'-Pa$ in the elderly was significantly greater than in the young, and greater than in the elderly receiving isoflurane (table IV). The gradient between $PE'$ and $Pa$ for volatile anaesthetic agents is proportional to the $PI-Pa$ gradient and is greater for agents of greater solubility [27]. The greater $PE'-Pa$ gradient for halothane in the elderly than in the young may be explained by the greater $PI-Pa$ gradient and greater $\dot{V}/\dot{Q}$ inequality in the elderly [2, 12, 27].

The blood/gas partition coefficient for isoflurane was significantly less in the elderly and there was a similar trend for halothane (not statistically significant). Lower blood/gas partition coefficients in the elderly have been noted previously by Lerman and colleagues and may be a result of smaller plasma concentrations of albumin in this age group [6]. The blood/gas partition coefficients we found for isoflurane are similar to those found by Lerman's group, but our values for halothane are slightly greater than theirs (2.65 in the young, 2.41 in the elderly).

The smaller $Pa_{CO_2}$ values in the halothane group suggest a greater arterial to end-tidal gradient for carbon dioxide in subjects receiving halothane. However, because the halothane part of the study was carried out after isoflurane, it is impossible to say whether this reflected a real difference between the agents or a difference in the instruments for measuring $PE'_{CO_2}$ and $Pa_{CO_2}$.

The elderly are a heterogenous population and our data apply only to healthy elderly patients. In elderly patients with coexisting disease, the likely effect of pathological processes on washin of isoflurane and halothane must be considered in conjunction with the data presented here.

## ACKNOWLEDGEMENTS

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# EFFECT OF INSPIRED OXYGEN CONCENTRATION ON THE INCIDENCE OF DESATURATION IN PATIENTS UNDERGOING TOTAL HIP REPLACEMENT

B. AL-SHAIKH

**SUMMARY**

*The effect of inspired oxygen concentration on the incidence of desaturation was studied in two groups of patients ($n = 32$ and $31$) during total hip replacement. During insertion of acrylic bone cement, those patients receiving an inspired fractional oxygen concentration ($F_{I_{O_2}}$) of 0.5 had less desaturation (3%) than those receiving an $F_{I_{O_2}}$ of 0.33 (34%).*

**KEY WORDS**

*Complications: hypoxaemia. Oxygen: $F_{I_{O_2}}$. Surgery: total hip replacement.*

There have been several reports of complications, including hypoxaemia, associated with the insertion of acrylic bone cement (polymethylmethacrylate) during hip arthroplasty [1–3].

The present study was designed to compare the effects of an $F_{I_{O_2}}$ of 0.5 and one of 0.33 on the incidence of desaturation during insertion of cement in total hip replacement.

## PATIENTS AND METHODS

Sixty-three ASA I or II patients undergoing total hip replacement surgery were studied. The study was approved by the Hospital Ethics Committee and informed written consent was obtained from each patient. All patients were premedicated with papaveretum 0.3 mg kg$^{-1}$ and hyoscine 0.006 mg kg$^{-1}$ i.m. 1 h before operation. Anaesthesia was induced with thiopentone 4–5 mg kg$^{-1}$. Tracheal intubation was facilitated with vecuronium 0.1 mg kg$^{-1}$; the lungs were ventilated mechanically, and anaesthesia was maintained with nitrous oxide and 1–1.5% enflurane in oxygen. All patients were monitored using pulse oximetry ($Sp_{O_2}$), non-invasive arterial pressure (SAP) and $F_{I_{O_2}}$ (Cardiocap, Datex). The patients were positioned for surgery in the lateral position on a horizontal table with the pulse oximeter probe positioned on the non-dependent ear. The patients were allocated randomly to two groups: group I ($n = 32$) received an $F_{I_{O_2}}$ of 0.33 throughout the whole procedure, while in group II ($n = 31$) $F_{I_{O_2}}$ was increased to 0.5 at least 10 min before insertion of the cement and continued for a further 10 min after the insertion of the cement for each of the acetabular and femoral components (table I).

TABLE I. *Patient characteristics (mean (range or SD))*

| $F_{I_{O_2}}$ | $n$ | Age (yr) | Weight (kg) | Sex (M/F) |
|---|---|---|---|---|
| 0.33 | 32 | 69.4 (65–73) | 72.1 (8.5) | 10/22 |
| 0.5 | 31 | 71.2 (67–74) | 70.8 (9.6) | 12/19 |

The increase in $F_{I_{O_2}}$ from 0.33 to 0.5 in group II was timed in co-ordination with the surgical and nursing staff. The acetabular component was always inserted first, followed by the femoral component. In group II, after insertion of the acetabular component, $F_{I_{O_2}}$ was restored to 0.33 and increased to 0.5 10 min before insertion of the femoral component. The femoral cement was inserted using a cement gun, without venting of the shaft. SAP and $Sp_{O_2}$ were measured at 1-min intervals for 10 min before and 10 min after the

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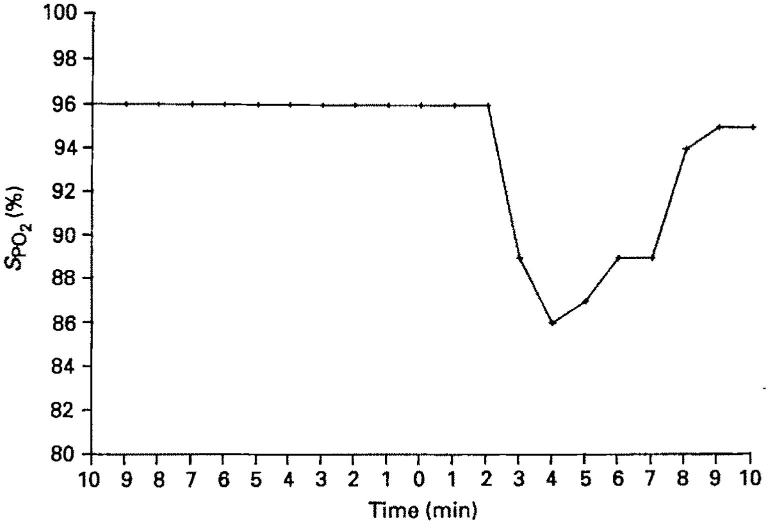

FIG. 1. Decrease in $Sp_{O_2}$ as the cement was inserted in the femoral component in a patient in group I.

insertion of cement for both components. Measurements were continued beyond 10 min if changes in $Sp_{O_2}$ were of longer duration (two patients in group I).

A persistent decrease of 2 % or greater in $Sp_{O_2}$ and a decrease of 10 % or greater in arterial pressure was considered a clinically significant event. Data were analysed using chi-square with Yates' correction and Mann–Whitney $U$ test as appropriate. $P < 0.05$ was considered statistically significant.

## RESULTS

Eleven patients (34 %) in group I had a decrease in $Sp_{O_2}$ during insertion of the cement. Only one patient (3 %) in group II had a decrease in $Sp_{O_2}$ during insertion of the cement for a femoral component. Table II shows the incidence of the reduction in $Sp_{O_2}$ (2 % or more) in both groups during insertion of the cement of the acetabular, femoral or both components of the total hip arthroplasty. The maximum decrease in $Sp_{O_2}$ was 10 % in group I and 2 % in group II.

TABLE II. *Number of patients in each group with a decrease in $Sp_{O_2}$ of 2 % or greater during insertion of the cement of the acetabular, femoral or both components of the total hip replacement. * Changes more frequent* ($P < 0.05$) *than in group II*

| Group | *n* | Acetabulum | Femoral | Both | Total |
|---|---|---|---|---|---|
| I | 32 | 2 | 7 | 2 | 11 (34.37 %)* |
| II | 31 | 0 | 1 | 0 | 1 (3.22 %) |

The decrease in $Sp_{O_2}$ occurred within 1–4 min (median 1 (SD 0.93) min) after insertion of the cement and lasted for 5–25 min (median 9.5 (SD 5.92) min). The only episodes of decrease in $Sp_{O_2}$ were associated with cement insertion, in both groups throughout the operation.

There was no relation between the incidence or degree of reduction in $Sp_{O_2}$ and the general medical condition of the patients ($P = 0.576$) or the habit of smoking ($P = 0.925$) in each group.

In both groups, a decrease in $Sp_{O_2}$ did not correlate with a decrease in arterial pressure ($P = 0.85$) (table III). The decreases in SAP lasted for 1–2 min and recovered without treatment.

## DISCUSSION

This study has demonstrated a decrease in $Sp_{O_2}$ following insertion of cement during total hip replacement in about 30 % of patients when an $F_{I_{O_2}}$ of 0.33 was used. The greatest decrease in $Sp_{O_2}$ was 10 % (from 96 % to 86 %) (fig. 1); this occurred during the insertion of cement for the femoral component, but there were no associated changes in arterial pressure in this healthy, non-smoking patient.

The pathophysiological mechanisms responsible for these changes in $Sp_{O_2}$ are not clear. Previous work had suggested that cement entering the circulation causes sudden and transient

TABLE III. *Numbers of patients in each group who had a decrease in SAP during the insertion of the cement and a decrease in both SAP and* $Sp_{O_2}$

| | Patients with decrease in SAP | | Patients with decrease in SAP and $Sp_{O_2}$ | | |
|---|---|---|---|---|---|
| | No. | Decrease (mm Hg) | No. | Dec. in SAP (mm Hg) | Dec. in $Sp_{O_2}$ (%) |
| Acetabular | | | | | |
| Group I | 13 | 9–22 | 1 | 10 | 3 |
| Group II | 4 | 9–16 | 0 | | |
| Femoral | | | | | |
| Group I | 15 | 15–31 | 2 | 15, 28 | 6, 3 |
| Group II | 7 | 10–15 | 1 | 12 | 2 |

changes in the pulmonary vasculature [2]. Others have suggested that the release of tissue-thromboplastic products into the circulation causes intravascular coagulation and respiratory reaction [3]. It has also been suggested that microembolization of air and fat occurs with denaturing of the proteins of the blood draining the area, because of the heat produced during polymerization of the cement, with the release of intracellular components into the circulation [4].

The incidence and severity of the reduction in $Sp_{O_2}$ were greater with the insertion of the femoral component than the acetabular component, as shown by previous workers [1–3]. This could be caused by various factors, including the larger surface area and the higher vascularity of the femoral shaft with the very high pressures generated as the cement sets [1]. Intramedullary pressure may increase to more than 500 mm Hg during cemented implants [5]. Another factor may be that the amount of cement used for the femoral component is about twice that used for the acetabular component.

Our observation that utilization of an $FI_{O_2}$ of 0.5 decreased significantly the incidence of desaturation, implies that the desaturation caused by insertion of the cement was caused by ventilation–perfusion inequalities rather than an increase in the true right–left shunt [6]. Changes in arterial pressure after insertion of cement had no effect on changes in $Sp_{O_2}$ and this is in agreement with previous studies [2]. The arterial pressure changes were transient, whereas the duration of desaturation lasted up to 25 min. Similar observations have been described previously [3, 7].

Within the clinical range, arterial oxygen saturation is measured accurately by pulse oximetry [8]. Positioning the pulse oximeter probe on the non-dependent ear is likely to reflect arterial oxygenation more reliably than the fingers, as acute changes in $Sp_{O_2}$ may be delayed by 30–60 s in the finger compared with the ear [9]. Pulse oximeters are also less reliable during transient severe desaturation as their programs average and compute the input in order to reject any artefacts.

These results indicate that increasing $FI_{O_2}$ to 0.5 during the insertion of cement in total hip arthroplasty is to be recommended.

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# HEART RATE RESPONSE TO AN I.V. TEST DOSE OF ADRENALINE AND LIGNOCAINE WITH AND WITHOUT ATROPINE PRETREATMENT

P. NARCHI, J.-X. MAZOIT, S. COHEN AND K. SAMII

### SUMMARY

*In order to evaluate the sensitivity of an adrenaline test dose for detecting intravascular injection and the effect of atropine pretreatment, 90 ASA physical status I and II patients were allocated randomly to two groups, to receive i.v. saline 1 ml ($n = 46$) or i.v. atropine 0.5 mg ($n = 44$). Five minutes later, all patients received an i.v. test dose of 2% lignocaine 3 ml with adrenaline 15 μg at a rate of 1 ml $s^{-1}$. The groups were similar with respect to basal heart rate (HR). HR remained unchanged after saline injection, but increased slightly 5 min after atropine injection (mean 78 (SD 15) beat $min^{-1}$ vs 87 (20) beat $min^{-1}$ ($P < 0.05$). After the test dose of lignocaine with adrenaline, HR increased significantly in both groups at 30 s, 1 and 2 min, and remained increased at 3 min in the atropine group. The maximum increase in HR was greater in the atropine group than in the saline group (31 (4) beat $min^{-1}$ vs 26 (11) beat $min^{-1}$ ($P < 0.05$). However, when individual maximum HR changes are considered, five patients in the saline group and four in the atropine group had an increase $\leqslant 10$ beat $min^{-1}$, and three patients in the saline group had no change or a decrease in HR. Defining a positive result to a test dose as an increase in HR of $> 10$ beat $min^{-1}$, the sensitivity of the adrenaline test dose was 83 (5.5)% in the saline group and 91 (3.5)% in the atropine group (ns). Thus a test dose containing 2% lignocaine 3 ml and adrenaline 15 μg was not very sensitive for detecting intravascular injection, as moderate or false negative responses occurred frequently.*

**KEY WORDS**

*Anaesthesia: i.v. regional, test dose. Nerve, vagus: atropine Sympathetic nervous system: adrenaline.*

Regional blocks often require the use of large doses of local anaesthetics which, if accidentally injected i.v., may cause serious neurological and cardiovascular toxicity [1]. An i.v. test dose containing adrenaline 15 μg induced a consistent increase in heart rate in the 175 patients studied by Moore and Batra and therefore has been proposed as an effective means of detecting an i.v. injection [2]. However, subsequent publications have questioned the validity of an adrenaline test dose in parturients [3–5]. To be useful, a test dose must be both specific and sensitive. The lack of specificity has already been demonstrated in parturients who exhibited false positive responses to an adrenaline test dose (increases in HR after i.v. injection of bupivacaine without adrenaline) [6]. No data are available on the sensitivity of this test in non-pregnant adults, whereas the lack of sensitivity (false negative responses) has been reported in children anaesthetized with halothane [7]. Occasionally, atropine may be given before a regional block is performed, to prevent vagal attacks [8]; this may itself increase heart rate and modify the response to the test dose. The aim of this study, therefore, was to measure individual heart rate response to an i.v. adrenaline test dose with and without atropine pretreatment, in order to evaluate its sensitivity.

## PATIENTS AND METHODS

The study was approved by the local Committee on Human Research, and informed consent was

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obtained from 90 ASA physical status I or II patients. Patients receiving beta-blockers, calcium channel blockers or other anti-arrhythmic drugs were excluded from the study. Thirty-four patients received no premedication, and 66 received hydroxyzine 100 mg orally 2 h before surgery.

In the operating theatre, a cannula was inserted into a suitable vein and Ringer's lactate solution was infused i.v. at a rate of 100 ml $h^{-1}$. Heart rate (HR) was measured continuously from the digital output of the ECG (lead 2). Systolic arterial pressure (SAP) was monitored using an automatic device (Dinamap). Five minutes later, patients received, in a random manner, either i.v. saline 1 ml ($n = 46$) or i.v. atropine 0.5 mg in 1 ml of saline ($n = 44$). Five minutes after this, patients in both groups received a test dose of 2 % lignocaine 3 ml with adrenaline 15 µg injected i.v. at a rate of 1 ml $s^{-1}$ as described previously [2]. HR was measured before and 5 min after injection of saline or atropine and 30 s, 1, 2 and 3 min after the test dose. In addition, the ECG was observed continuously and the maximum change in HR after test dose injection was recorded for each patient. SAP was measured before and 5 min after either saline or atropine and then 1, 2 and 3 min after the test dose injection. Any side effects were also noted.

Data were analysed using the chi-square test or Student's *t* test to compare patients characteristics and basal HR. Changes in HR and SAP within and between groups were compared using one- or two-way repeated measures analysis of variance followed by a *t* test or Newman–Keuls test as appropriate. Results are expressed as the mean (SD). $P < 0.05$ was considered statistically significant.

## RESULTS

The groups were similar in age, gender distribution, premedication and basal HR (table I). Mean HR remained unchanged after saline injection, whereas it increased by 9 beat $min^{-1}$ ($P < 0.05$) in the atropine group (fig. 1). Following the test dose, HR increased significantly in both groups; this change lasted for 2 min in the saline group and 3 min in the atropine group (fig. 1). Maximum change in HR occurred in all patients, within 2 min of test dose injection (fig. 2). The mean maximum increase in HR was significantly greater in the atropine group than in the saline group: 31 (14) beat $min^{-1}$ *vs* 26 (15) beat $min^{-1}$ ($P < 0.05$). There was considerable variation in both groups. The increase in HR was moderate ( $\leqslant 10$ beat $min^{-1}$) in five patients in the saline group and four patients in the atropine group. Furthermore, in the saline group, HR was unchanged in one patient and actually decreased in two patients. No correlation was found between the increase in HR and either basal HR or the increase in HR in

TABLE I. *Patient characteristics (mean (range or* SD*)). No statistical difference between the groups*

| | Saline group | Atropine group |
|---|---|---|
| *n* | 46 | 44 |
| Age (yr) | 47 (19–83) | 46 (13–76) |
| Sex (M/F) | 21/25 | 21/23 |
| Premedication | | |
| None | 16 | 18 |
| Hydroxyzine | 30 | 26 |
| Basal HR (beat $min^{-1}$) | 84 (15) | 78 (15) |

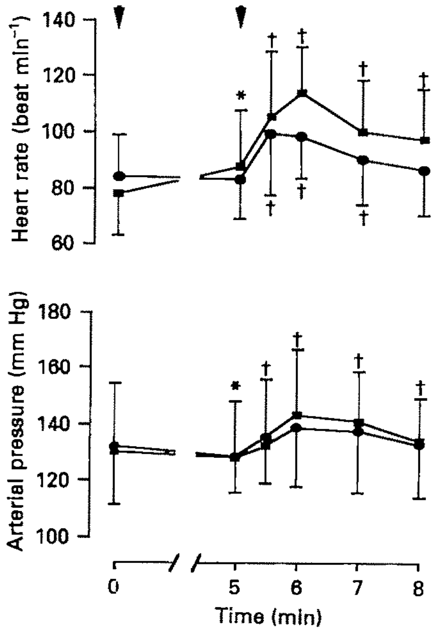

FIG. 1. Mean (SD) changes in heart rate (upper part) and systolic arterial pressure (lower part) 5 min after injection of saline (●) or atropine (■) (first arrow) and 30 s, 1, 2 and 3 min after injection of adrenaline test dose (second arrow). $P < 0.05$ compared with: * before saline or atropine; † before adrenaline test dose (calculated using the total population for arterial pressure, as ANOVA failed to find any difference between the two groups).

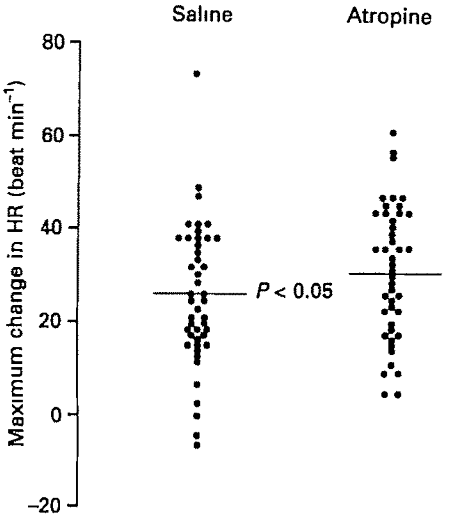

FIG. 2. Individual and mean values of maximum change in heart rate (HR) following i.v. injection of test dose in the saline and atropine groups.

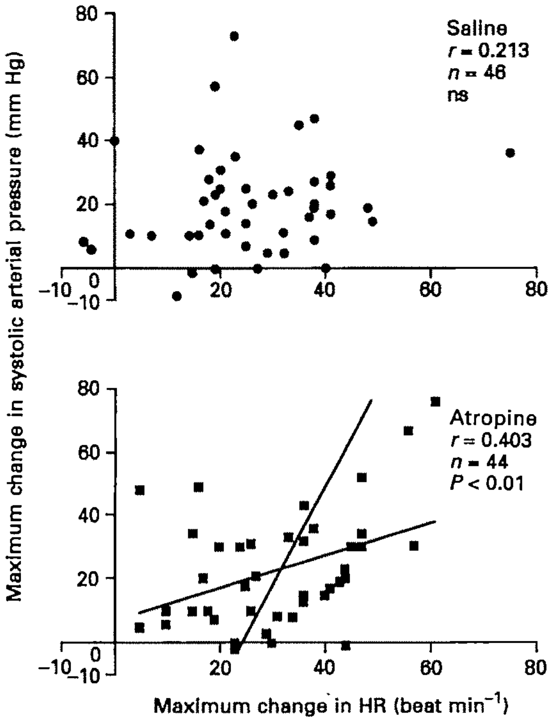

FIG. 3. Correlation between the observed maximum change in systolic arterial pressure and the observed maximum change in heart rate (HR). No statistical correlation in the saline group, but significant correlation in the atropine group ($r = 0.403$ for both regression lines).

response to atropine, and there were no correlations between the absence of a significant increase in HR after test dose and age, sex or premedication.

There was no difference in increase in SAP between the two groups (ANOVA). However, a small but significant decrease in SAP was observed 5 min after saline or atropine injection (fig. 1). After adrenaline test dose injection, SAP increased significantly (fig. 1), but the correlation between the observed maximum increase in SAP and the observed maximum increase in HR was significant only in the atropine group (fig. 3). Side effects frequently occurred after i.v. injection of adrenaline. Fourteen patients in the saline group, and 19 patients in the atropine group complained of minor side effects such as palpitations, shivering, dizziness, headache and a sensation of heat. Seven patients in the saline group and five in the atropine group exhibited arrhythmias on the ECG (premature ventricular contraction or atrial tachycardia).

## DISCUSSION

This study was designed to evaluate the sensitivity of an adrenaline test dose for detecting intravascular injection, and to determine if prior administration of atropine affected its sensitivity.

After i.v. test dose injection, in the saline group we observed a significant increase in HR within 2 min. The mean maximum HR increase of 26 (15) beat $\text{min}^{-1}$ is close to the 32-beat $\text{min}^{-1}$ increase reported by Moore and Batra [2]. However, because a test is useful only if it is highly sensitive (has a low rate of false negative responses), individual rather than mean responses must be considered.

In our study there was considerable individual variation in the HR change. As spontaneous changes in HR may occur during a block because of emotion, we believe that an increase in HR must exceed 10 beat $\text{min}^{-1}$ in order to be clinically significant. Using this criterion, eight patients of 46 in the saline group had a false negative response to the adrenaline test dose, which represent a sensitivity of 83 (5.5)% compared with 91 (13.5)% in the atropine group (ns). Moore and Batra reported a consistent increase in HR in 175 patients who received an adrenaline test dose; only three patients who were taking beta-adrenergic blockers had negative responses [2]. Because individual values were not reported in their study, the frequency of no change or only a moderate increase in heart rate is unknown. Using a study design similar to ours, Desparmet and colleagues [7] found that an adrenaline test dose did not induce a reliable increase in heart rate in children anaesthetized with halothane and nitrous oxide. They reported an increase in heart rate of less than 10 beat min$^{-1}$ in six of 21 children after a test dose (sensitivity 72 (10) %).

This inconsistent increase in HR after i.v. injection of a test dose may be explained by the fact that adrenaline affects HR by two opposing mechanisms: stimulation of beta-adrenoreceptors leading to an increase in HR and stimulation of alpha-adrenoreceptors leading to an increase in arterial pressure; this stimulates baroreceptor reflexes, leading to a decrease in HR [9]. This indirectly mediated bradycardia may attenuate the direct chronotropic effect of adrenaline. Atropine may partially counteract bradycardia induced by adrenaline and this might explain the greater degree of tachycardia and the significant correlation between HR and SAP increases observed after test dose injection in the atropine group, compared with the saline group. However, despite an increase in HR in every patient in the atropine group, this was less than or equal to 10 beat min$^{-1}$ in four patients—almost 10 % of patients. Desparmet also found that pretreatment with atropine improved the reliability of an adrenaline test dose in anaesthetized children, but did not ensure total reliability [7]. A false negative response occurred in one of 20 children studied.

We designed our study to represent our usual clinical practice as closely as possible. Atropine 0.5 mg is used routinely in our institution before an extradural block is performed, in order to prevent vagal bradycardia. The tachycardia observed following this dose has been observed elsewhere in similar conditions, and is usually sustained for at least 10–15 min [10, 11].

The occurrence of ECG abnormalities in only 12 % of the patients studied is considerably less than the 50 % incidence reported previously in a similar study [2]. The other side effects observed were minor and infrequent, perhaps because of the relative youth and physical condition of the patients.

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# BIOCHEMICAL ASSESSMENT OF PREOPERATIVE STRESS: A STUDY WITH DIAZEPAM AND MEASUREMENT OF MONOAMINE METABOLITES AND CATECHOLAMINES IN CEREBROSPINAL FLUID AND PLASMA

J. KANTO AND M. SCHEININ

## SUMMARY

*Diazepam 5 mg or an inert placebo tablet was given as preoperative hypnotic on the night before operation to two groups (n = 18 in each) of healthy women having elective Caesarean section under spinal analgesia. A third group (n = 18) received no hypnotic. The quality of the preoperative night's sleep assessed subjectively was significantly better in the diazepam-treated patients compared with those receiving no drug. The diazepam-treated patients had also smaller CSF concentrations of noradrenaline (NA) and of the dopamine metabolite, 3,4-dihydroxyphenylacetic acid (DOPAC). In comparison with the two other patient groups, in the diazepam group there was no correlation between demographic, physiological or subjectively estimated variables and CSF or plasma measurements of monoamine transmitters and their metabolites. Preoperative fear and apprehension correlated most strongly with preoperative heart rate and with the increase in heart rate from the previous day. The monoamine neurotransmitters or their metabolites were of limited use in monitoring the intensity of preoperative fear and anxiety.*

***KEY WORDS***

*Cerebrospinal fluid · monoamine concentrations. Hypnotics, benzodiazepine: diazepam Sympathetic nervous system activation*

Anxiety before anaesthesia and surgery is associated with increased secretion of stress-related hormones, for example adrenaline and cortisol [1, 2]. We have investigated previously the relationship between situational anxiety before surgery and monoamine turnover in the central nervous system (CNS) by measuring monoamine metabolite concentrations in samples of cerebrospinal fluid (CSF) and plasma in healthy patients undergoing Caesarean section under spinal analgesia without premedication [3]. Contrary to our expectations, self-perceived anxiety was clearly associated only with circulatory changes, and catecholamine and monoamine metabolite concentrations in CSF and plasma were poor indicators of preoperative anxiety [3]. However, the subjectively estimated poor quality of the preoperative night's sleep correlated with biochemical plasma and CSF measures of increased sympathoadrenal activity [3]. In the present study we have evaluated these associations further, with special reference to the effects of diazepam or an inert placebo tablet taken on the night before surgery.

## MATERIALS AND METHODS

### *Subjects and procedure*

Fifty-four healthy pregnant women at or near term (37–41 weeks) gave informed consent to the study, which was approved by the local Ethics Committee. The patients were undergoing elective Caesarean section for obstetric reasons, usually fetopelvic disproportion. The pregnancy was uncomplicated in all cases (apart from the need for surgical delivery) and no patient was receiving any medications (except iron salts and vitamins). Arterial pressure and heart rate were recorded on the ward after at least 30 min rest on

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the night before surgery. In group 1 ($n = 18$) the patients received no premedication; in group 2 ($n = 18$) a placebo tablet was given at 22:00 (11 (SD 1) h before surgery); in group 3 ($n = 18$) a 5-mg diazepam tablet was given 11 (1) h before surgery. The patients in groups 2 and 3 were blinded to the medications. The patients were allocated randomly to the three groups on the ward, and the anaesthetist (J.K.) was not aware of the groupings. However, two patients in group 1 reported spontaneously on the lack of premedication.

Surgery was performed with the patient under spinal analgesia. An infusion of Ringer's lactate was given i.v. via a large vein in the right antecubital fossa. After resting for a minimum of 30 min, just before induction of spinal anaesthesia, the patient was asked to grade the quality of the previous night's sleep and the feelings of preoperative fear and apprehension, on 100-mm visual analogue scales (VAS) (without ticks). The extremes on the scale for quality of sleep were "very poor" (= 0 mm) and "very good" (= 100 mm) and those for fear and apprehension "none at all" (= 0 mm) and "worst possible" (= 100 mm).

Arterial pressure (AP) and heart rate (HR) were measured at 5-min intervals using an oscillotonometer (Cardiocap, Datex, Finland). The greatest preoperative values were used for comparison with the previous night's recordings. Immediately before subarachnoid block was induced, a sample of venous blood was obtained from the i.v. cannula. A 25-gauge needle was then inserted at L2–3 into the subarachnoid space, with the patient in the lateral decubitus position, and 1.8–2.3 ml of CSF aspirated slowly into a pre-cooled polypropylene syringe and replaced with bupivacaine. The CSF was transferred rapidly to polycarbonate tubes, chilled on ice, centrifuged briefly at +4 °C and stored at −70 °C together with the plasma samples.

### *Biochemical methods*

The concentrations in CSF of the major CNS metabolites of the monoamine neurotransmitters noradrenaline (NA), serotonin (5-HT), and dopamine (DA)—that is, 3-methoxy-4-hydroxyphenylglycol (MHPG; metabolite of NA), 5-hydroxyindoleacetic acid (5-HIAA; metabolite of 5-HT) and homovanillic acid (HVA; metabolite of DA) were measured using high pressure liquid chromatography (HPLC) with electrochemical detection [4]. Concentrations of NA and adrenaline, the NA metabolite 3,4-dihydroxyphenylglycol (DHPG) and the DA metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) in plasma and CSF were measured also using HPLC, after extraction on activated alumina [5].

### *Statistical analysis*

Data were analysed using Amstat One and Two programs (GJ & SC Coleman, 1985 and 1986, U.K.) run on an Amstrad 128-K microcomputer. Student's *t* test, analysis of variance (ANOVA), and linear regression analysis were used for parametric variables; non-parametric data were evaluated with the Kruskal–Wallis test, Mann–Whitney *U* test, and Spearman's rank order correlations.

## RESULTS

There were no significant differences between the three patient groups in age, weight or height (one-way ANOVA) (table I). The patients in the diazepam group estimated their quality of sleep as significantly better than did those patients who did not receive tablets (Kruskal–Wallis test, $P = 0.034$; Mann–Whitney $U$ test, $P = 0.014$). However, there was no significant difference between the placebo and diazepam groups. There was no significant difference between the three patient groups with respect to preoperative fear and apprehension, and no significant difference between the groups in HR, in the increase of HR from the previous night, or in arterial pressure. However, fear and apprehension were correlated significantly with preoperative HR (Spearman's rank order correlations: no hypnotic agent $r = 0.58$, $P = 0.011$; placebo $r = 0.57$, $P = 0.012$; diazepam $r = 0.46$, $P = 0.050$), and with increase in HR ($r = 0.63$, $P = 0.005$; $r = 0.58$, $P = 0.027$; $r = 0.61$, $P = 0.007$, respectively).

The CSF concentrations of NA and DOPAC were significantly smaller in the group receiving diazepam than in the non-premedicated group (ANOVA, followed by Student's $t$ test: $P = 0.027$ and $P = 0.0075$) (table II). DOPAC concentration was also smaller in the placebo group than in the non-premedicated group ($P = 0.050$). MHPG concentrations in CSF were greater in group 2, compared with both group 1 ($P = 0.015$) and group 3 ($P = 0.034$). Plasma concentrations did not differ significantly between groups.

In groups 1 and 2, there were several significant (although often relatively low) correlations be-

TABLE I. *Patient characteristics, the patients' subjective estimates of the quality of sleep on the night before surgery and feelings of preoperative fear and apprehension (visual analogue scales), preoperative heart rate (HR) and its increase from the previous day's value (mean (SD)). Significant difference between groups 1 and 3 in quality of sleep* (P = *0.014*)

| | Age (yr) | Weight (kg) | Height (cm) | Score on VAS 0–100 Sleep | Score on VAS 0–100 Fear | HR (beat min$^{-1}$) | Increase in HR (beat min$^{-1}$) |
|---|---|---|---|---|---|---|---|
| No medication | 29.8 | 72.6 | 162.2 | 47.2 | 49.4 | 99.4 | 18.9 |
| (group 1) | (4.2) | (8.3) | (3.3) | (27.8) | (24.4) | (13.6) | (12.2) |
| Placebo | 30.9 | 73.6 | 163.5 | 61.1 | 53.3 | 102.7 | 19.9 |
| (group 2) | (4.6) | (9.4) | (5.6) | (21.1) | (20.0) | (14.2) | (11.5) |
| Diazepam 5 mg | 28.1 | 73.8 | 162.4 | 69.4 | 58.3 | 98.7 | 17.5 |
| (group 3) | (4.0) | (9.4) | (6.1) | (24.8) | (24.8) | (12.7) | (8.7) |

TABLE II. *Concentrations (mean (SD)) of noradrenaline (NA) and its metabolites, 3,4-dihydroxyphenylglycol (DHPG) and 3-methoxy-4-hydroxyphenylglycol (MHPG), the dopamine metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), and the main metabolite of serotonin (5-HT), 5-hydroxyindoleacetic acid (5-HIAA) in CSF; concentrations of NA, DHPG, adrenaline (A) and DOPAC in plasma. Significant differences : CSF NA—group 1* vs *group 3* (P = *0.027*)*; CSF DOPAC—group 1* vs *group 3* (P = *0.0075*)*, group 1* vs *group 2* (P = *0.050*)*; CSF MHPG—group 1* vs *group 2* (P = *0.015*)*; group 2* vs *group 3* (P = *0.034*)

| | Concentration (nmol litre$^{-1}$) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | CSF | | | | | | Plasma | | | |
| | NA | DHPG | MHPG | DOPAC | HVA | 5-HIAA | NA | DHPG | A | DOPAC |
| No medication | 1.55 | 13.4 | 42.0 | 5.8 | 206 | 128 | 1.23 | 5.3 | 0.15 | 15.5 |
| (group 1) | (0.54) | (5.0) | (7.8) | (2.6) | (43) | (31) | (0.50) | (1.6) | (0.10) | (5.6) |
| Placebo | 1.50 | 12.0 | 47.8 | 3.6 | 226 | 178 | 1.27 | 6.2 | 0.15 | 16.4 |
| (group 2) | (0.54) | (2.1) | (6.7) | (1.3) | (88) | (69) | (0.50) | (1.1) | (0.11) | (7.1) |
| Diazepam 5 mg | 1.09 | 10.4 | 41.6 | 3.3 | 206 | 149 | 1.34 | 5.9 | 0.24 | 17.9 |
| (group 3) | (0.56) | (4.5) | (9.9) | (1.2) | (60) | (64) | (0.04) | (1.4) | (0.18) | (6.9) |

tween patient characteristics, physiological and subjectively estimated variables and different CSF or plasma measurements. For example, body height correlated negatively in groups 1 and 2 with the concentrations of the acidic monoamine metabolites DOPAC, HVA and 5-HIAA in CSF. Similar relationships were not detected in the diazepam-treated patients. The most consistent of these associations appeared to be a negative correlation between quality of sleep and CSF concentrations of NA and its metabolites in the non-premedicated group (NA: $r = -0.61$, $P = 0.007$; DHPG: $r = -0.54$, $P = 0.04$; MHPG: $r = -0.57$, $P = 0.03$). In contrast, these correlations were not significant in groups 2 and 3.

There were also many significant interrelationships between the CSF and plasma measurements in groups 1 and 2, but not as many in group 3. For example, the CSF and plasma concentrations of NA and its metabolites showed significant positive intercorrelations in groups 1 and 2; the greatest correlations were between NA and DHPG in CSF ($r = 0.84$ and $r = 0.73$). NA and adrenaline concentrations in plasma were significantly correlated only in group 1 ($r = 0.60$, $P = 0.02$). All acidic monoamine metabolite concentrations in CSF were positively intercorrelated, but again only in groups 1 and 2.

## DISCUSSION

The patients receiving diazepam 5 mg orally on the night preceding surgery slept significantly better than those who did not receive medication. This difference was associated with significantly smaller CSF concentrations of NA and the dopamine metabolite DOPAC in the diazepam group. However, the use of diazepam as a hypnotic had no effect on subjective perception of preoperative anxiety or circulatory variables. Poor quality of sleep was associated with biochemical signs of increased noradrenergic activity in the group receiving no hypnotic, which corroborates our earlier results [3]. Interestingly, in both the diazepam and the placebo groups there was no negative association between quality of sleep and the CSF concentrations of NA and its metabolites DHPG and MHPG. On the whole, diazepam appeared to perturb many of the associations observed between the patient characteristics, physiological or subjectively estimated variables and the different CSF or plasma measurements; this was not the case with placebo treatment. Similarly, administration of diazepam was not associated with many of the normal intercorrelations between the CSF and plasma concentrations of the different monoamine neurotransmitters and their metabolites. In our opinion, reduced sympathoadrenal activation in the diazepam-treated patients is the most likely explanation for the three phenomena. This is supported by previous findings of positive correlations between anxiety and CSF NA and MHPG concentrations in depressed patients [6, 7].

The negative association of body height with the concentration of 5-HIAA in lumbar CSF and the positive correlations between the acidic monoamine metabolites, 5-HIAA, DOPAC and HVA in CSF have been reported previously [8, 9]. Interestingly, diazepam treatment appeared to abolish these associations.

In our previous study, we found that poor quality of sleep during the preoperative night was associated with increased NA and MHPG concentrations in CSF and NA and adrenaline in plasma in patients without any drug treatment [3]. This may lead to disturbances of cardiac rhythm and suggests, therefore, that benzodiazepines are useful for the treatment of situational preoperative insomnia [10, 11].

The limited usefulness of hormones and monoamines and their metabolites as outcome measures has been observed in earlier clinical premedication studies with anxiolytic agents [3, 5, 12–14]. In spite of many statistically significant correlations between preoperative anxiety and CSF or plasma concentrations, few clinically useful associations have been observed. Thus subjective VAS assessments or simple measurements of HR or the increase in HR or arterial pressure from the previous day [3] appear to be more useful and reliable indicators of the severity of preoperative anxiety than the biochemical measurements undertaken here.

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# COMPARISON OF FLUMAZENIL WITH AMINOPHYLLINE TO ANTAGONIZE MIDAZOLAM IN ELDERLY PATIENTS

A. N. SIBAI, A. M. SIBAI AND A. BARAKA

## SUMMARY

*We have compared, in a double-blind study, the efficacy of flumazenil with that of aminophylline in antagonizing the effects of midazolam in 60 patients (ASA I–II, mean age 66 yr) undergoing transurethral resection of prostate under spinal anaesthesia. All patients received midazolam 0.075 mg $kg^{-1}$ i.v. and the test drugs were given 5 min after its administration. Patients were allocated randomly to receive i.v. flumazenil 0.01 mg $kg^{-1}$, aminophylline 2 mg $kg^{-1}$ or placebo saline 0.1 ml $kg^{-1}$. One minute after administration, aminophylline caused 42% reversal of sedation, 66% of disorientation and 73% of lack of co-operation in comparison with placebo, although there was marked individual variation. Flumazenil caused complete and rapid antagonism of sedation, disorientation and lack of co-operation.*

**KEY WORDS**

*Hypnotics: midazolam. Antagonists: flumazenil, aminophylline, theophylline.*

Flumazenil (Anexate) has been introduced recently into clinical practice as a specific benzodiazepine receptor antagonist. Aminophylline, a non-specific central nervous system (CNS) stimulant drug, has been shown to antagonize the sedation induced by benzodiazepine derivatives such as flurazepam [1], lorazepam [2] and diazepam [3, 4]. Stirt [3] has suggested that aminophylline may also be useful in antagonizing midazolam sedation, but this was not confirmed by Sleigh [5] and Mathews and colleagues [6]. The purpose of our study was to compare the effects of flumazenil with those of aminophylline in antagonizing the actions of midazolam.

## PATIENTS AND METHODS

The study was approved by the local Ethics Committee and informed consent was obtained from all patients, who comprised admissions for transurethral resection of prostate (TURP). The following patients were excluded: ASA III and above; insulin-dependent diabetics; patients receiving benzodiazepine derivatives, aminophylline, sedative or stimulant CNS drugs; those suffering from impaired memory, hearing or consciousness; and patients with renal or hepatic insufficiency, cardiac problems or chronic obstructive pulmonary disease.

Sixty male patients, ASA I and II, were allocated randomly to three groups ($n = 20$) to receive flumazenil, aminophylline or placebo. All patients were premedicated with glycopyrrolate 0.3 mg i.m., 1 h before operation. In the anaesthetic room, a cannula was inserted into a peripheral vein and Hartmann's solution infused i.v. All patients received a spinal block via the L2–3 or L3–4 lumbar interspace with amethocaine 4–5 ml. In the operating room, patients were placed in the lithotomy position for TURP. Arterial pressure, heart rate and ECG were monitored.

Patients received an i.v. bolus of midazolam 0.075 mg $kg^{-1}$. Five minutes later, flumazenil 0.01 mg $kg^{-1}$, aminophylline 2 mg $kg^{-1}$ or saline 0.1 ml $kg^{-1}$ was given randomly as an i.v. bolus in a double-blind manner. The volume and the colour of the three solutions were comparable. During operation, any hypotension was treated with

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TABLE I. *Evaluation of the codes used to score the central nervous system variables: sedation, disorientation and lack of co-operation. A greater score indicates improved antagonism for the three outcome variables*

| Scale | Description |
|---|---|
| Sedation | |
| 0 | Asleep and not responding to painful stimuli (pinching) |
| 1 | Asleep and responding to painful stimuli |
| 2 | Asleep and responding to verbal order |
| 3 | Awake and drowsy |
| 4 | Fully awake |
| Disorientation to space and time (Where are you? What day is it today?) | |
| 0 | Fully disoriented |
| 1 | Partially oriented |
| 2 | Fully oriented |
| Lack of co-operation and collaboration (Lift your hand, with or without imitation) | |
| 0 | Fully unco-operative (order not executed) |
| 1 | Partially co-operative (order executed by imitation) |
| 2 | Fully co-operative (order executed by verbal command) |

increments of i.v. phenylephrine hydrochloride 100 µg. Blood loss was replaced adequately.

### *Measured variables*

CNS variables were measured according to Nisbet and Norris [7] and Ricou and colleagues [8], with modifications as presented in table I. Baseline data recorded before and after spinal block included the level of wakefulness, orientation and co-operation. Scores for sedation, disorientation and lack of co-operation were noted at 1, 3 and 5 min after administration of midazolam, and at 1, 3, 5, 10, 15, 20, 25, 30, 35, 40, 45, 60, 90 and 120 min after the administration of the test drug or placebo.

### *Statistics*

Data were analysed statistically using the Mann–Whitney *U* test. Cochran's method of analysis of comparison of slopes was used to compare the course of action of aminophylline with that of midazolam following their threshold effects. All data are presented as mean (SD). $P < 0.05$ was considered significant.

## RESULTS

The ages of the patients included in this study were 50–86 yr (mean 66 yr). Patients had a mean ASA score of 1.6 (0.5). There was no significant difference in age, weight, height or ASA score between the three groups (table II).

Figure 1 compares the actions of flumazenil, aminophylline and placebo on sedation, which was maximal (grand mean (SD) ($n = 60$) 1.1 (0.52)) 5 min after administration of midazolam. One minute after flumazenil, patients in this group ($n = 20$) were fully awake, with no incidence of anxiety (mean score 4 (0)). This was maintained with minimal non-significant variations thereafter. At 1 min, the mean sedation score of patients in the aminophylline group was 2.35 (1)—an increase of 42% antagonism of sedation in comparison with placebo (saline). At 35 min, there was no significant difference in the sedation score between flumazenil and aminophylline ($P = 0.146$), and at 45 min there was no significant difference in the score between placebo and either flumazenil ($P = 0.378$) or aminophylline ($P = 0.176$).

TABLE II. *Characteristics of patients in the three groups (mean (range or* SD*)). No significant differences between groups (Mann–Whitney* U *test)*

| | Group I Flumazenil ($n = 20$) | Group II Aminophylline ($n = 20$) | Group III Placebo ($n = 20$) |
|---|---|---|---|
| Age (yr) | 67 (57–86) | 66 (50–78) | 66 (51–83) |
| Weight (kg) | 72 (9) | 73 (1) | 69 (11) |
| Height (cm) | 169 (8) | 167 (5) | 166 (7) |
| ASA (I–II) | 1.5 (0.5) | 1.4 (0.5) | 1.6 (0.4) |

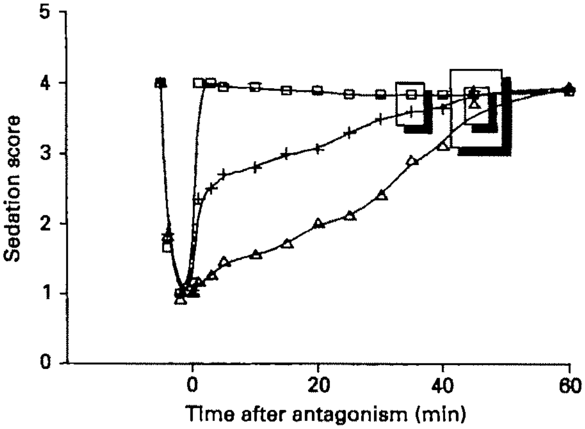

FIG. 1. Mean sedation score in the flumazenil (□), aminophylline (+) and placebo (△) groups. Shaded boxes indicate timings at which comparisons between each pair of the groups were not significant ($P > 0.05$, Mann–Whitney): at 35 min for comparison between flumazenil and aminophylline groups, and at 45 min for comparison between the placebo and either flumazenil or aminophylline groups.

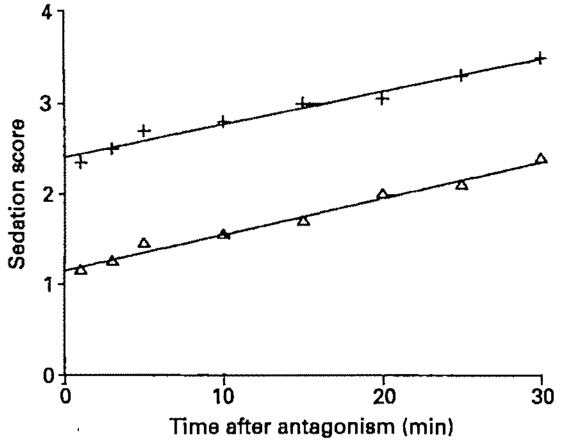

FIG. 2. Regression analysis of mean sedation score for aminophylline (+) and placebo (△) against time. No significant difference between regression slopes ($P > 0.05$).

Figure 2 represents the regression lines obtained when mean sedation scores for aminophylline and placebo were plotted against time. The data presented were restricted to those obtained 1–30 min after administration of antagonist. Using Cochran's method of analysis, there was no significant difference in the slopes of both regression lines ($P > 0.05$).

Figures 3 and 4 present the actions of flumazenil, aminophylline and placebo on disorientation and lack of co-operation, respectively. Maximum disorientation and lack of co-operation (grand mean (SD) ($n = 60$): 0.23 (0.48) and 0.22 (0.51)) occurred 5 min after administration of midazolam. One minute after flumazenil, there was full orientation and co-operation of all patients in this group ($n = 20$) (mean score of 2 (0)) and this was maintained thereafter. At 1 min, the disorientation and unco-operation scores of aminophylline were 1.45 (0.89) and 1.55 (0.83), respectively—an increase of 66 % antagonism of disorientation and an increase of 73 % antagonism of lack of co-operation in comparison with those in the placebo group. At 20 min, there was no significant difference between aminophylline and placebo in both disorientation and lack of co-operation scores ($P = 0.249$ and $P = 0.12$, respectively). At 15 and 25 min, there was no significant difference in the lack of co-operation and disorientation scores between the flumazenil and aminophylline groups ($P = 0.154$ and $P = 0.324$, respectively). At 30 and 35 min, there was no significant difference in the lack of co-operation and disorientation scores between the flumazenil and placebo groups ($P = 0.13$ and $P = 0.154$, respectively).

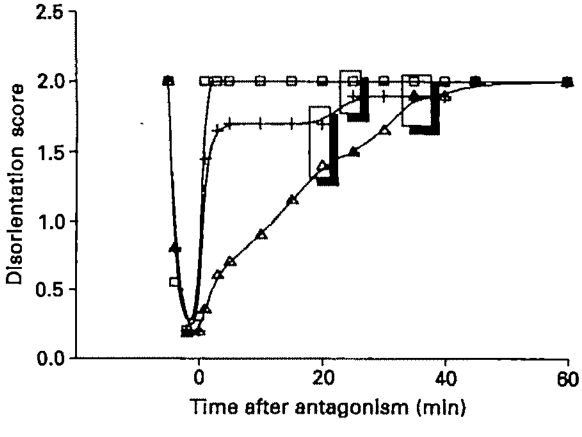

FIG. 3. Mean disorientation score in the flumazenil (□), aminophylline (+) and placebo (△) groups. Shaded boxes indicate timings at which comparisons between each pair of the groups were not significant ($P > 0.05$, Mann–Whitney): at 20 min for comparison between aminophylline and placebo groups, at 25 min for comparison between flumazenil and aminophylline groups, and at 35 min for comparison between flumazenil and placebo groups.

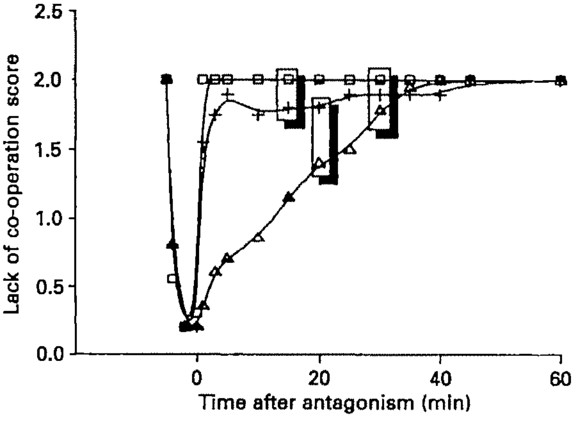

FIG. 4. Mean lack of co-operation score in the flumazenil (□), aminophylline (+) and placebo (△) groups. Shaded boxes indicate timings at which comparisons between each pair of the groups were not significant ($P > 0.05$, Mann–Whitney): at 15 min for comparison between flumazenil and aminophylline groups, at 20 min for comparison between aminophylline and placebo groups, and at 30 min for comparison between flumazenil and placebo groups.

## DISCUSSION

The present report has demonstrated the effect of flumazenil and aminophylline in antagonizing the action of midazolam, in the absence of other possible factors that may affect the action of midazolam. Flumazenil scores for sedation, disorientation and lack of co-operation were greatest (with zero SD) 1 min after its administration. None of the patients in the flumazenil group had anxiety. This is in contrast with the study by Ricou and colleagues [8] (around 20% incidence of anxiety), in which flumazenil was used in a dose 10 times larger than that used in the present study.

In the aminophylline group, the mean sedation score at 1 min was moderate, with a large SD in comparison with that for flumazenil, indicating variation in responses to aminophylline. Subsequently, there was a gradual increase in the aminophylline score in parallel with the sedation score of placebo. This suggests that a ceiling effect of aminophylline was achieved at 1 min, and any further improvement was related probably to redistribution and metabolism of midazolam. This is in contrast with other reports. Sleigh's letter [5] suffered several limitations, of which the most important was that his patients were studied under uncontrolled conditions. Mathews and colleagues [6] reported on patients under general anaesthesia using oxygen–nitrous oxide–isoflurane. The dose of midazolam used for induction of anaesthesia was 0.3 mg kg$^{-1}$; this is significantly larger than the sedative dose of midazolam 0.075 mg kg$^{-1}$ used in our study. Aminophylline is a non-specific CNS stimulant drug and its stimulant action may not be revealed if the patient is over sedated, or other depressant drugs have been used. Aminophylline has been reported to antagonize morphine- [9] and fentanyl- [10] induced respiratory depression and to reduce the depth and duration of sedation by thiopentone [11]. However, it does not alter the anaesthetic requirement for halothane [12]. It has also been used for treatment of neonatal apnoea [13] and Cheyne–Stoke ventilation [14].

Midazolam interacts with specific high-affinity binding sites for benzodiazepines [15], and benzodiazepine derivatives potentiate the inhibitory effect of $\gamma$-amino butyric acid (GABA) [16, 17]. In contrast, although flumazenil is an imidazodiazepine, it has no benzodiazepine action [18]. It is a specific competitive benzodiazepine antagonist [19].

Aminophylline is a complex of theophylline and ethylenediamine. Its main action is competitive inhibition of the depressant action of endogenous adenosine [20]. In addition, ethylenediamine is known to interact with the binding of [H$^3$] diazepam in the cerebral cortical synaptosomal membrane [21]. This may explain the moderate and non-specific effect of aminophylline in counteracting the action of midazolam.

## ACKNOWLEDGEMENT

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# SPINAL ANAESTHESIA IN OBSTETRICS

## I. G. KESTIN

Spinal anaesthesia in obstetrics differs from spinal anaesthesia in non-pregnant patients in several ways. Smaller doses of local anaesthetic are needed for spinal anaesthesia in pregnancy, and the spread in cerebrospinal fluid (CSF) is less predictable. Hypotension, spinal headache and spinal opioid side effects are more common in pregnant patients than general surgical patients. The fetus may be affected adversely by maternal hypotension or inappropriate vasopressors. Technical difficulty in finding the subarachnoid space may be greater in pregnancy because of the increased lumbar lordosis.

This article summarizes the physiology and pharmacology of spinal anaesthesia during pregnancy and reviews current clinical practice and recent developments.

### PHYSIOLOGY AND PHARMACOLOGY

Smaller doses of local anaesthetics are used for spinal anaesthesia during pregnancy. For example, the mean height of the block after plain 0.5% bupivacaine 2.5 ml in pregnant patients was T2 [125]. Using a similar technique in general surgical patients, the mean height of the block after plain 0.5% bupivacaine 3 ml was L1 [37]. Four hypotheses have been proposed to explain this.

*Change in CSF volume.* Inferior vena caval (IVC) compression during pregnancy causes extradural venous engorgement, which may reduce lumbar CSF volume [70]. Local anaesthetic injected into this reduced CSF volume may spread to higher segmental levels than in non-pregnant patients; CSF volumes have never been measured during pregnancy, but several studies indirectly support this hypothesis.

Barclay and colleagues investigated the effects of IVC compression on the level of spinal anaesthesia in three groups: obstetric patients for Caesarean section, gynaecological patients (controls) and gynaecological patients who had an abdominal binder applied just before spinal anaesthesia [20]. The same technique of spinal anaesthesia was used in the three groups. The obstetric and abdominal binder groups had a similar and significantly higher level of block than the controls, and the level of block varied more widely in these two groups than in the controls. Reduction in CSF volume is the most likely explanation for the similar results in the obstetric patients and the gynaecological patients with an abdominal binder.

CSF pressures during pregnancy and labour are within the normal range [76, 98, 139], and an increase in IVC pressure caused only a transient increase in CSF pressure [20]. The absence of any significant alterations in CSF pressure during labour and delivery suggests that the fluctuations in lumbar extradural venous volume may be accommodated by reciprocal changes in CSF volume.

Assali and Prystowski studied the cardiovascular response to sympathetic block during pregnancy [15]; they used an intrathecal catheter to give the injections into the CSF after positioning their patients supine. They found a three- to four-fold reduction in dose compared with postpartum studies in the same patients. The patients lay supine without left tilt or uterine displacement, so IVC compression, extradural venous engorgement and lumbar CSF reduction would have been at a maximum. Under these conditions, a large difference of 300–400% was found between doses

*KEY WORDS*
*Anaesthesia: obstetric. Anaesthetic techniques: extradural, spinal.*

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required for spinal anaesthesia pre- and postpartum. If aortocaval compression were avoided, the reduction in CSF volume may be less, and less difference might be expected between pre- and postpartum dose requirements. This was observed in the study by Abouleish, who reported only a 30% difference in dose requirements between pre- and postpartum situations [8].

*Cephalad displacement of local anaesthetic.* An increase in extradural venous volume *after* intrathecal injection of local anaesthetic may displace CSF and local anaesthetic to higher segmental levels. Cephalad displacement of CSF has been observed during diagnostic myelography, when abdominal compression caused cephalad movement of dye [20]. Russell used 0.5% plain bupivacaine for spinal anaesthesia for Caesarean section, and found that the spread of the block with the patient *in the lateral position* was similar to that in non-pregnant patients [121]. There was a marked cephalad extension of the block when the patients were moved from the lateral to the supine position, and only then did the block extend sufficiently to permit Caesarean section [121]. A similar, but smaller, effect has been demonstrated also in non-pregnant patients [122].

*Change in CSF composition.* Protein composition of CSF during pregnancy is normal [97], so reduced binding of local anaesthetics is unlikely to explain the reduction in dose requirements.

*Increased sensitivity of nerve fibres to local anaesthetic.* The sensitivity of nerve fibres to local anaesthetics is altered during pregnancy. Using the vagus nerve from pregnant and non-pregnant rabbits, Datta and colleagues showed that the sensitivity of A and C fibres to local anaesthetics was increased, and the onset of block was more rapid during pregnancy [50, 64]. The susceptibility of human peripheral nerves to lignocaine was increased during pregnancy [28]. The hormonal changes during pregnancy have been proposed as the cause for the altered pharmacodynamics and the lesser dose requirements for spinal anaesthesia [50]. CSF concentrations of progesterone in humans are increased during pregnancy and immediately postpartum, and there was a correlation between CSF concentration of progesterone and dose requirements for intrathecal lignocaine [48].

### *Postpartum studies*

There is a gradual change in the response to spinal anaesthesia during the first 3 days postpartum [95]. DeSimone and colleagues reported a small decrease in the average height of the block in postpartum patients compared with patients undergoing Caesarean section, from T1 to T3 [52]. There was no correlation between height of block in the postpartum patients and time after delivery [52]. Another similar study reported that 30% more bupivacaine was needed to achieve a similar height of block in postpartum patients compared with patients having Caesarean section [8].

### *Miscellaneous factors*

CSF volume must be related to the size of the patient, but this is not a factor of clinical importance for choosing the dose of local anaesthetic for spinal anaesthesia. The spread of hyperbaric bupivacaine in patients undergoing Caesarean section was found not to correlate with height, weight, length of vertebral column or body mass index of the patient [110, 111].

Some authors believe that an intrathecal injection should not be given during a uterine contraction, because turbulence in the CSF may affect the spread unpredictably [43, 66, 98]. Hopkins and colleagues reported that the height of the block was unaffected by the phase of the uterine contraction cycle in which the spinal injection was given [76]. Coughing after intrathecal injection does not affect spread [58]. The timing of an intrathecal injection during labour is therefore probably of no clinical importance.

The 22-gauge Whitacre spinal needle has a pencil point with a side opening that directs the intrathecal injection. The direction of injection should be lateral or cephalad to obtain adequate sensory block for Caesarean section [69]. However, most obstetric anaesthetists believe that a needle size larger than 25 gauge should not be used in obstetrics.

## CLINICAL ASPECTS

Spinal anaesthesia may be more difficult in pregnancy because of the increase in lumbar lordosis. The lateral approach may be easier [1], and an oblique approach may also help to decrease the incidence of spinal headache [119]. It is important to keep the bevel of Quincke needles facing laterally to decrease the incidence of spinal headache [93].

There are three types of spinal block in pregnancy: saddle block of the sacral roots only, suitable for low outlet forceps delivery and perineal operations; low spinal block of the sacral, lumbar and thoracic roots as far as T10, suitable for instrumental deliveries; mid spinal block of the sacral, lumbar and thoracic roots as far as T4, suitable for Caesarean section [103].

The anaesthetist's biggest challenge is to provide safe spinal anaesthesia for Caesarean section.

### *Caesarean Section*

Spinal block is still the most frequent choice of anaesthetic for Caesarean section in the U.S.A. [68], and it is becoming increasingly popular in the U.K.

If the injection is given with the patient in the lateral position, it is important that the patient is in the right lateral position, and then turned supine with a left tilt or manual uterine displacement. The anaesthesia may be inadequate on one side if injection is made with the patient in the left lateral position, and then turned supine with a left tilt or uterine displacement; this has been shown for both hyperbaric and isobaric solutions [34, 123, 132]. Clinical experience suggests that satisfactory blocks may be obtained with hyperbaric solutions when patients are in the sitting position. It may be wise to lay the mother on her right side before positioning her supine with a left tilt. The relationships between baricity, positioning and spread during pregnancy have not been evaluated fully.

Hyperbaric 0.5 % bupivacaine is now the only local anaesthetic licensed in the U.K. for intrathecal injection, although plain 0.5 % bupivacaine is used commonly. Bupivacaine, in common with amethocaine, is a relatively insoluble local anaesthetic and precipitates in CSF at a concentration of 830 $\mu g\ ml^{-1}$ [59]. Theoretically, this concentration would be reached with bupivacaine 15 mg after equilibration in the CSF below T5 [59]. The concentrations of bupivacaine in CSF measured in clinical practice have been much smaller—between 150 and 420 $\mu g\ ml^{-1}$ [21, 51, 100, 107]. Bupivacaine concentrations in CSF during pregnancy may be greater if the CSF volume is reduced. The solubility of bupivacaine would be reduced further by respiratory alkalosis from maternal hyperventilation. It is not known if precipitation of bupivacaine in CSF is clinically important in obstetrics.

Plain 0.5 % bupivacaine has a baricity of 0.999 at 37 °C [70] and is regarded widely as an isobaric preparation. In theory, the position of the patient during and after the block should not affect the spread of isobaric solutions within the CSF. There are two reasons why this is not true for plain 0.5 % bupivacaine in obstetrics. First, plain 0.5 % bupivacaine is slightly hypobaric [37, 129]. Second, movement of pregnant patients has a considerable effect on the height of the spinal block with plain bupivacaine [121]. Russell gave plain 0.5 % bupivacaine for Caesarean section to patients who lay on their sides for the intrathecal injection, and only after the patient was moved from lateral to supine did the anaesthesia extend sufficiently for surgery [121].

Russell and Holmqvist compared spinal anaesthesia for Caesarean section in two groups, using either 2.5 ml of isobaric or 2.5 ml of hyperbaric 0.5 % bupivacaine [125]. The onset of analgesia, maximum spread and duration of analgesia were similar in both groups. This differs from the usual finding that hyperbaric solutions spread further and have a shorter duration than the same dose of isobaric solutions [37, 114, 129, 140]. The authors suggested that displacement of CSF and bupivacaine during positioning of the patient moved the isobaric bupivacaine cephalad, but not the hyperbaric solution. The viscous hyperbaric solution may layer in the dependent regions of the subarachnoid space, mix less with the CSF, and be displaced less readily cephalad than the isobaric solution. Administration of 2.5 ml of either solution produced satisfactory anaesthesia for Caesarean section, and this dose of bupivacaine has been used satisfactorily in many other studies [34, 53, 83, 101]. If 2 ml or less of 0.5 % bupivacaine is used, there is a substantial risk of inadequate block [124, 126]. The quality of the block with 0.75 % bupivacaine was better if adrenaline was added [9], but this concentration of bupivacaine is not available in the U.K.

An incremental technique of spinal anaesthesia using plain 0.5 % bupivacaine through a 32-gauge catheter has been compared with extradural anaesthesia for Caesarean section [86]. The intrathecal catheter was placed, and a satisfactory block established, more quickly. The quality of the block and haemodynamic stability were similar for the two techniques. The total dose of intrathecal bupivacaine was very variable (mean 2.1 ml, range 1.5–7.4 ml), but the height of the block was controlled within a narrow range of segments by the incremental technique (range T3–T5).

### *Combined spinal and extradural anaesthesia*

Brownridge first reported this technique; he inserted an extradural catheter at L1–2 and then gave a spinal at L3–4 [26]. The extradural catheter was used to extend the block and for postoperative analgesia. Other workers have first identified the extradural space with a Tuohy needle, used this as an introducer for the spinal needle, given the intrathecal injection, and then inserted an extradural catheter [32, 54, 89, 106, 118]. The advantages claimed for the combination technique are rapidity of onset and density of the spinal block, combined with the ability to extend the block and provide postoperative analgesia with the extradural catheter. Rawal, Schollin and Wesstrom reported that intraoperative analgesia during Caesarean section was better with a combined technique than with extradural anaesthesia alone [118]. Brownridge used the extradural catheter for postoperative analgesia in 200 patients, and there were no spinal headaches [26]. Further studies are needed to determine the true incidence of spinal headache after a combined technique; if the incidence of headache is confirmed to be very low, the combined technique may be better than either spinal or extradural anaesthesia alone.

A combined extradural and spinal technique may be used for Caesarean section if an extradural block is inadequate after giving the maximum dose of local anaesthetic. Blood concentrations of local anaesthetic are often high after extradural analgesia during labour and then Caesarean section [135]. A spinal block may extend the extradural block and avoid general anaesthesia. The peak plasma bupivacaine concentration after intrathecal bupivacaine 20 mg is 20–30 ng $ml^{-1}$ [17], and an increase in blood concentration of this magnitude should not cause toxicity. Combined techniques have been reviewed recently by Carrie [33].

### *Combined local anaesthetic and opioid spinal anaesthesia for Caesarean section*

Spinal local anaesthetics and opioids have synergistic antinociceptive effects in animal studies [14], and there have been several studies of spinal anaesthesia for Caesarean section using bupivacaine with opioid [3, 11, 36, 78, 81, 94, 104, 143]. Between 0.1 mg [3] and 0.6 mg [143] of morphine has been added to bupivacaine for spinal anaesthesia, and the duration of analgesia after Caesarean section was 18–24 h. Most studies report that the duration of analgesia and incidence of side effects after intrathecal morphine depend on the dose. Abouleish and colleagues [11] measured oxygen saturation after operation, and Abboud and colleagues [3] measured carbon dioxide response curves after operation. The respiratory effects of morphine were more frequent and severe in patients receiving parenteral morphine compared with intrathecal morphine. Chadwick and Ready compared intrathecal with extradural morphine, and found the frequency and severity of adverse effects were similar for the two techniques [36].

The quality of the block during surgery was better using intrathecal bupivacaine with morphine compared with bupivacaine alone [1]. This is difficult to explain, because intrathecal morphine has a slow onset of 30–90 min [7, 12, 19]. Lipophilic opioids have a more rapid onset, and there have been some recent preliminary reports using intrathecal fentanyl [78, 81, 94, 104]. Hunt and colleagues added between 6 and 30 μg of fentanyl to bupivacaine for spinal anaesthesia for Caesarean section [78]. Postoperative analgesia lasted only 2 h, and did not depend on the dose of fentanyl. There were more side effects with larger doses of fentanyl. Other workers have reported that postoperative analgesia in both pregnant and non-pregnant patients was not prolonged by adding fentanyl to local anaesthetics for spinal anaesthesia [94, 108]. Studies to determine if adrenaline prolongs analgesia after intrathecal local anaesthetics with fentanyl have produced conflicting results [81, 94]. Malinow and colleagues compared intrathecal lignocaine and fentanyl 10 μg with and without adrenaline for postpartum tubal ligation, and reported that the duration of postoperative analgesia was doubled and the incidence of pruritis was reduced by adding adrenaline [94]. Johnson and colleagues added adrenaline to bupivacaine and fentanyl 10 μg for Caesarean section; conversely, they reported that the duration of postoperative analgesia was not increased, motor block was prolonged, and nausea and vomiting were more common after adrenaline had been added [81].

Naulty compared bupivacaine with fentanyl 5 μg and morphine 0.1 mg, bupivacaine with morphine 0.2 mg, and bupivacaine alone for spinal anaesthesia for Caesarean section [104].

The bupivacaine with fentanyl and morphine gave a long duration of postoperative analgesia compared with bupivacaine alone; compared with bupivacaine with morphine 0.2 mg, intraoperative analgesia was better, postoperative analgesia lasted as long, and opioid side effects were reduced [104]. Pethidine has both opioid and local anaesthetic properties, and has been tried as the sole intrathecal anaesthetic for Caesarean section [134], but the results were poor; analgesia was of short duration, hypotension was often severe and side effects were common.

Pregnant patients are more at risk of suffering from spinal opioid side effects [25], and opioid antagonists have been used to alleviate these effects. Naltrexone is a long acting opioid antagonist that can be given orally; patients who received it after intrathecal bupivacaine with morphine for Caesarean section had less effective analgesia, but the same incidence and severity of side effects [112].

Many of these studies of combinations of drugs have appeared only as preliminary communications, whilst the peer reviewed articles have reported only relatively few patients. There is no consensus yet about the optimum drug, the dose, the risks or the requisite monitoring, but promising results have been obtained using small doses of fentanyl and morphine combined with bupivacaine.

### *Hypotension*

Hypotension during spinal anaesthesia is common, rapid in onset and has adverse effects on both mother and fetus. The principal causes are rapid block of the sympathetic nerves and aortocaval compression.

Vasopressors and i.v. fluids are used for prophylaxis and treatment of hypotension during spinal anaesthesia. Many studies have shown the advantages of fluid loading before spinal block [39, 96, 99] and this is now standard practice. Volumes larger than 1 litre are more effective; infants had less acidaemia if their mothers had been given more than 1 litre of crystalloid before the spinal than if the mothers had received less than 1 litre [31]. Colloids are not used commonly for fluid loading; the gelatin solutions and dextrans are not recommended because of allergic reactions [16]. Five percent albumin (15 ml $kg^{-1}$) was a very effective prophylaxis against hypotension [99], but expense precludes routine use of this technique.

Ephedrine is used in clinical practice because animal studies have shown that uterine blood flow is maintained better with ephedrine than with other vasopressors, including dopamine [29, 61, 79, 116, 120, 130]. Jouppila and colleagues measured uterine blood flow during spinal anaesthesia for Caesarean section; uterine blood flow was maintained if hypotension was avoided by giving i.v. ephedrine [83]. Several authors have used i.m. ephedrine as prophylaxis against hypotension during spinal anaesthesia [71, 99, 126]. The best result obtained by this method was a 7% incidence of hypotension [126]. I.v. ephedrine is more effective in avoiding hypotension, and should be given as soon as any reduction in arterial pressure is noticed. Ephedrine has been given as boluses [46, 49] or an infusion (50 mg in 500 ml of crystalloid), the rate of which was adjusted to maintain systolic pressure [83, 85]. None of the patients in these studies developed hypotension [46, 49, 83, 85]. Maternal nausea and vomiting were significantly reduced if hypotension was avoided by this early use of ephedrine [46, 85].

To summarize these results, the best prophylaxis against hypotension comprises: an infusion of crystalloid 1.5–2 litre before the spinal block; an i.v. infusion of ephedrine 50 mg in crystalloid 500 ml, adjusted to maintain systolic pressure; i.v. boluses of ephedrine as soon as any decrease in arterial pressure is recorded.

### *Infant Condition after Caesarean Section during Spinal Anaesthesia*

The principal adverse effect on the fetus is prolonged maternal hypotension [31, 60, 96]. The fetus is not harmed if hypotension is treated promptly and effectively. Corke and colleagues showed that even hypotension of short duration (less than 2 min) caused some fetal acidaemia, but other measures of fetal health were not affected [39]. Norris confirmed that the fetus is not harmed if hypotension during spinal anaesthesia is treated promptly [109]. Placental blood flow is preserved during spinal anaesthesia for Caesarean section if hypotension is avoided [83, 90]. Jouppila and colleagues studied one patient with pre-eclampsia; after spinal anaesthesia, placental blood flow increased by 193%, an increase similar to that produced during extradural anaesthesia [83, 84].

Studies have shown consistently that infants born by Caesarean section under spinal anaesthesia are in better condition than those born under general anaesthesia [5, 75, 96]. This advantage extended into the first few hours of life, but by 24 h, there was no difference in infant behaviour between those born during extradural, spinal or general anaesthesia [5].

It is particularly important to avoid hypotension if the mother is diabetic. Hypotension during spinal anaesthesia for Caesarean section caused more severe acidaemia in infants of diabetic mothers than in infants of healthy mothers [47]. A subsequent study from the same institution reported that spinal anaesthesia could be given safely to diabetic mothers, provided hypotension was avoided and maternal blood sugar concentrations were controlled [49]. Dextrose-containing fluids should not be used for fluid loading before spinal anaesthesia in mothers with diabetes, as fetal acidaemia has been shown to be greater after maternal hypotension in the presence of hyperglycaemia [47, 49].

### *Spinal anaesthesia compared with extradural anaesthesia*

Caritas and colleagues compared infants born by Caesarean section under extradural or spinal anaesthesia [31]. Spinal anaesthesia was associated with more severe maternal hypotension and more acidaemia in these infants at delivery. The infants born during spinal anaesthesia to those mothers who did *not* have any hypotension were similar to those born during extradural anaesthesia [31].

If local anaesthetics had an adverse effect on the infant after delivery, spinal anaesthesia might be a better choice than extradural anaesthesia because of the lower doses. Three possible adverse effects of local anaesthetics on the infant have been studied: behavioural adaptation, jaundice and myocardial depression. Infants have been studied with behavioural tests in the first few days of life to determine if local anaesthetics affect adaptation [2, 5, 75, 80, 87, 127]. The original report that lignocaine had an adverse effect on infant behaviour [127] has not been confirmed by subsequent studies [2, 87]. Abboud and colleagues studied the behaviour of infants born by Caesarean section during spinal or extradural anaesthesia [5]. There were no differences at delivery or at 24 h of age; 2 h after delivery, those born during spinal anaesthesia scored better than those born during extradural anaesthesia in tests of motor activity and supporting reactions [5]. The clinical significance of small and transient changes in scores for different neonatal behavioural tests is unknown; neonates born by normal vaginal delivery have a period of diminished alertness after approximately 1 h [55], and gender differences have been shown by some behavioural scales of neonatal responsiveness [88]. Jani and colleagues found no differences in the behaviour of infants born by Caesarean section under spinal or extradural anaesthesia [80].

An association between extradural anaesthesia during labour and neonatal jaundice has been reported [30]. Bupivacaine binds to red cell membranes, and so might increase haemolysis. Gale, Ferguson and Stevenson reported that neonatal bilirubin production was not increased after the mother had extradural anaesthesia with bupivacaine [67], and a large clinical study did not confirm there was an association between bupivacaine and neonatal jaundice [91]. Bupivacaine used for extradural anaesthesia does not cause clinically important myocardial depression in the neonate. Neonatal cardiac function, assessed by systolic time intervals, was similar in two groups of infants after Caesarean section during spinal or extradural anaesthesia [72]. There is no evidence that extradural or spinal anaesthesia is a better choice for the infant, provided the hypotension that is more common with spinal anaesthesia is avoided.

## *Headache*

The incidence of spinal headache reported in obstetric patients varies between 6% [105] and 16% [126]. The incidence of spinal headache in young non-pregnant women is also high, varying between 10% and 60% [62, 63, 137]. The high risk of spinal headache during pregnancy is probably associated with age and sex rather than pregnancy. Headache is a common symptom; 26.2% of pregnant patients had a headache after spinal anaesthesia, but only 33% of these were typical spinal headaches [27]. Twenty-five percent of these patients with spinal headaches had severe symptoms [27].

Needle size is an important determinant of the incidence of spinal headache [138]. There may be little to be gained by using spinal needles smaller than 26-gauge. There was no difference in the incidence of spinal headache with 26-gauge and 32-gauge needles [65], and 29-gauge needles are technically difficult to use [63].

The shape of the tip of the spinal needle alters the incidence of spinal headache. Needles with a conical tip are thought to separate the dural fibres instead of cutting them. A laboratory study showed that needles with conical tips caused less leakage across the dura than Quincke needles [119]. There are two spinal needles with conical tips: the 22-gauge Whitacre needle [74] and the 24-gauge Sprotte needle [133]. Both needles are associated with a smaller incidence of spinal headache compared with conventional spinal needles [35, 73, 133].

Severe headache after lumbar puncture may be caused by other mechanisms. Cortical venous thrombosis has occurred after spinal anaesthesia, and presented with symptoms and signs of a spinal headache [131].

Reasons which may account for the high incidence of spinal headache during pregnancy include: small CSF volume near term; decreased CSF pressure after delivery; peripartum dehydration; postpartum diuresis; early ambulation; anxiety; ligamentous changes; and bearing down at delivery [117].

*Small CSF volume.* There is no evidence that CSF volume is reduced during pregnancy (see above). CSF leakage after dural puncture with large diameter needles has been measured as 10 ml $h^{-1}$ *in vivo* [115]. In a laboratory study, the flow through the dura after puncture with a 25-gauge needle was 3.3 ml $min^{-1}$ [119], which is considerably more than the rate of production of CSF (0.3–0.4 ml $min^{-1}$) [44]. If this flow of CSF through the dura occurs *in vivo* after spinal anaesthesia with small needles, then CSF volume may be smaller than normal.

*Decreased CSF pressure after delivery.* CSF pressure is normal immediately after delivery [98]. There are no data on CSF pressures or volumes when spinal headaches develop later in the puerperium. The CSF pressure may be normal in patients with spinal headache [115].

*Peripartum dehydration and postpartum diuresis.* There is no evidence that either of these two factors causes the increased incidence of spinal headache in pregnancy. CSF formation is an active process, and it is doubtful if the rate of synthesis would be affected unless dehydration were severe. A high fluid intake is unlikely to affect CSF turnover, but urinary frequency may remind the patient of the postural headache.

*Early ambulation.* There is no prophylactic value in bed rest, for either pregnant [136] or non-pregnant patients [82].

*Bearing down during delivery.* Bearing down during the second stage made no difference to the incidence of spinal headache after spinal anaesthesia for vaginal delivery [27, 117].

### *Treatment*

Extradural blood patch is an effective treatment for spinal headache [27, 41]. Twenty-five percent of patients who had spinal headache experienced severe symptoms [27], and 1.6% of all patients after spinal anaesthesia for Caesarean section required a blood patch [105]. There is controversy about when an extradural blood patch should be undertaken after accidental dural puncture with a Tuohy needle. Therapeutic blood patches within 24 h had a much greater failure rate than those performed after 24 h [92], but early blood patches were shown to be an effective method of prophylaxis [38]. Prophylactic blood patches are probably not indicated after dural puncture with small diameter spinal needles; the incidence of spinal headache is low, and the headaches are often mild.

## *Intrathecal Opioids during Labour*

Yaksh and colleagues [141] first reported on the safety and efficacy of intrathecal opioids in animals, and subsequent clinical studies have investigated the effects of intrathecal opioids in humans.

The intrathecal route is preferable to the extradural route for spinal opioids in labour; extradural opioids do not produce consistent analgesia [23, 40, 77] and there is considerable systemic absorption [40].

Analgesia for the first stage of labour has been obtained with 0.2–2 mg of intrathecal morphine [4, 7, 12, 19, 45, 128]. The onset of analgesia was between 5 and 60 min and the duration 8–11 h [7, 19]. There were no effects on the cardiovascular system, progress of labour or fetus in any of these studies [4, 7, 19, 45, 128]. A recent abstract reported that mothers who received intrathecal morphine 0.2 mg had longer labours than mothers who had extradural bupivacaine [12]. If this is confirmed, it would obviously be a major clinical disadvantage of intrathecal morphine. Maternal plasma concentrations of β-endorphin decreased after analgesia with intrathecal morphine [4, 45]. An important disadvantage of intrathecal opioids is that analgesia for the second stage and operative procedures is poor, and additional methods of analgesia have often been necessary [7, 19].

Morphine has been used in all studies except that by Oyama and colleagues, who used intrathecal β-endorphin [113]. β-Endorphin has a large molecular weight and does not cross the blood–brain barrier or placenta. The analgesia was excellent, but there were the usual side effects.

Intrathecal opioids are probably the method of choice for analgesia during labour in mothers with severe cardiorespiratory disease. Abboud and colleagues gave intrathecal morphine 1 mg during labour to a mother with severe pulmonary hypertension; the mother had good analgesia with cardiovascular and respiratory stability [6]. A mother with symptomatic Wolfe–Parkinson–White syndrome had good pain relief and was haemodynamically stable after hyperbaric morphine 1 mg [24]. Ahmad and colleagues treated a patient with a univentricular heart, who presented in labour with severe cyanosis. She was given two intrathecal injections of morphine 1 mg during labour, with good results [13].

### *Adverse effects*

Maternal and fetal plasma concentrations of morphine are low after intrathecal morphine [22], and no adverse effect has been detected in the fetus at delivery [7, 19, 128] or at 24 h [19].

The most important risk for the mother is respiratory depression. Substances injected into the lumbar CSF reach the lateral and 4th ventricles after 3–6 h because of the normal CSF circulation [56, 57]. The factors that predispose to respiratory depression after intrathecal opioids are: old age, hydrophilic opioids, large doses, marked changes in thoracoabdominal pressures, lack of tolerance to opioids, and systemic administration of other opioid or CNS depressants [40]. These factors are not common in obstetrics, but Crawford suggested that intrathecal opioids are contraindicated unless the patient is in an intensive care unit [42]. There is one case report of late respiratory depression in an obstetric patient who had been given intrathecal morphine 1 mg [10]. Respiratory monitoring has shown that intrathecal morphine for analgesia after Caesarean section has less effect on respiration than parenteral morphine [3, 11]. Large prospective trials are needed to determine safe effective methods of analgesia and appropriate monitoring, both during labour and after Caesarean section.

There is a greater incidence of other opioid side effects in pregnant patients compared with non-pregnant patients [25], and some believe that this precludes the routine use of intrathecal opioids [102]. Pruritis is common (incidence ranges from 20% to 100% [19, 128]), dose dependent [7], and may last 30 h after a single injection [7]. The cause of pruritis after spinal opioids is not known. A sustained increase in plasma histamine concentration has been reported after intrathecal morphine for Caesarean section, but this did not correlate with the patients' symptoms [142]. A centrally mediated effect seems probable [18]. Drowsiness, nausea and vomiting, and urinary retention are also common, affecting 25–75% of patients [7, 19, 128]. Infusions of naloxone 0.4–0.6 mg $h^{-1}$ have been used to alleviate these side effects, with partial success [45]. The greater infusion rate diminished the analgesia.

Single injections of intrathecal morphine are not given commonly for analgesia during labour. Side effects are frequent, and the analgesia is poor during delivery or operative procedures. The advent of small diameter intrathecal catheters may lead to renewed interest in intrathecal opioids during labour. Small increments of opioids could be given, which should reduce the side effects, and local anaesthetics could be given if necessary.

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# COMPARISON OF ORTHODOX WITH FIBREOPTIC OROTRACHEAL INTUBATION UNDER TOTAL I.V. ANAESTHESIA

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## SUMMARY

*Fibreoptic orotracheal intubation was compared with orthodox laryngoscopy and tracheal intubation using a total i.v. technique with propofol in 60 ASA I and II patients. There was no significant difference between the two techniques in haemodynamic profile (before, during and following the intubation procedure) and incidence of postoperative sore throat. Minimal oxygen saturation was 96% during the study; maximal end-tidal* $P_{CO_2}$ *after intubation was 5.4 kPa. Intubation time was faster* ($P < 0.01$) *in the orthodox group (30.7 (SEM 2.3) s) than in the fibreoptic group (52.7 (4.8) s).*

### KEY WORDS

*Anaesthetics, intravenous: propofol. Intubation, tracheal: fibreoptic.*

Flexible fibreoptic instrumentation is a useful method of establishing a safe airway. It may become the method of choice for many anaesthetists rather than reserved for patients in whom rigid techniques have proven to be unsuccessful.

The haemodynamic stress response to oral fibreoptic intubation has been compared with that to conventional intubation in subjects anaesthetized with volatile agents. There was a significant difference in the haemodynamic responses of patients anaesthetized with halothane during orthodox compared with fibreoptic intubation; in contrast, there was no difference during enflurane anaesthesia [1, 2]. The objectives of the present study were to examine the cardiovascular responses to oral fibreoptic and orthodox intubation during total i.v. anaesthesia with propofol and to assess the incidence of postoperative sore throat.

## METHODS AND RESULTS

After approval by the local Ethics Committee and informed consent, we studied 60 patients (ASA I and II) undergoing elective ENT surgery. Patients taking antihypertensive medication and those with reflux, morbid obesity and airway pathology were excluded. The 60 patients were allocated to two groups. The first 30 underwent tracheal intubation orally with a Macintosh laryngoscope, while the other 30 underwent fibreoptic orotracheal intubation with an Olympus F6 bronchoscope. All patients were premedicated the night before with ranitidine 300 mg and 2 h before operation with midazolam 7.5 mg and atropine 1 mg orally. After arrival of the patient in the operating theatre, routine monitoring was commenced and an appropriate vein was cannulated.

Anaesthesia was induced as follows: fentanyl 0.2 mg i.v. was given to patients younger than 50 yr and fentanyl 0.1 mg i.v. to those of 50 yr and older; lignocaine 20 mg for local i.v. anaesthesia was administered with simultaneous infusion of propofol at a rate of 10 mg $kg^{-1}$ $h^{-1}$ and a propofol bolus of 1 mg $kg^{-1}$. As soon as adequate manual ventilation of the lungs was established, atracurium 0.5 mg $kg^{-1}$ was given i.v. Conventional or fibreoptic intubation was performed when neuromuscular block was complete (no visible reaction to train-of-four stimulation). All intubations were carried out by the authors.

Fibreoptic intubation was accomplished with the patient supine and the operator standing behind the patient's head. The bronchoscope,

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*This article is accompanied by Editorial II.*

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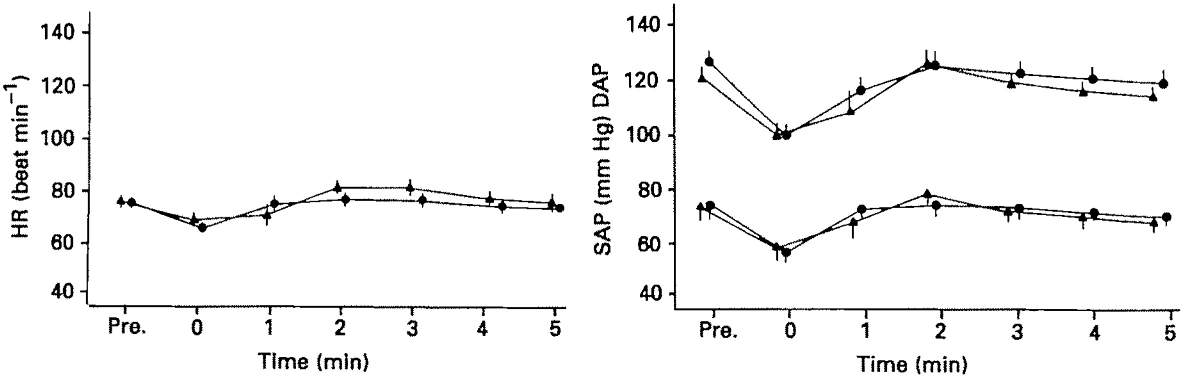

FIG. 1. Heart rate (HR) and systolic (SAP) and diastolic (DAP) arterial pressures (mean, SEM). Pre. = Last reading before induction; 0 = start of intubating procedure. ● = Intubated with laryngoscope; ▲ = intubated with fibreoptic bronchoscope.

with the tracheal tube mounted on it, was passed through the mouth and into the trachea with the jaw pulled forward by an assistant to open up the retropharyngeal space. The tip of the bronchoscope was positioned above the carina, the tracheal tube was slowly and carefully advanced into the trachea and the bronchoscope removed as soon as the position of the tube was confirmed visually to be about 2 cm above the carina.

The time between introduction of the laryngoscope or fibrescope until the first measurement of end-tidal carbon dioxide was recorded. Oxygen saturation was measured continuously.

Heart rate and systolic and diastolic arterial pressures were measured using a non-invasive pressure monitor (Mark III BP-103N) before induction of anaesthesia (control) and at 0, 1, 2, 3, 4 and 5 min after start of the intubation procedure. All patients were questioned after surgery for sore throat.

Data were analysed by chi-square, Student's *t* or Dutton's multiple comparison tests as appropriate. $P < 0.05$ was considered significant.

There were no significant differences in patient characteristics, in the haemodynamic profile during intubation (fig. 1) or incidence of postoperative sore throat. The time taken for fibreoptic intubation was significantly longer in the fibreoptic (52.7 (SEM 4.8) s) than in the conventional group (30.7 (2.3) s). Minimal oxygen saturation during the study period was 96 % in the fibreoptic and 97 % in the conventional group; maximal end-tidal $P\text{CO}_2$ after intubation was 5.2 and 5.4 kPa, respectively. Fifteen patients in the laryngoscopic and 16 patients in the fibreoptic group admitted to sore throat on questioning after operation.

## COMMENT

The magnitude of the stress response in this study was similar for conventional and fibreoptic intubation, confirming the findings of Finfer and colleagues [2]. A stable depth of anaesthesia for prolonged intubation is difficult to achieve with volatile agents without a ventilating mask, whereas continuous i.v. administration of a hypnotic agent is a simple method of guaranteeing a stable plasma concentration in spite of prolonged and sometimes recurrent periods of apnoea. We used propofol because of its pharmacological profile [3, 4]. There was no difference in mean arterial pressure after intubation compared with control values and heart rate increases of less than 10 beat $\text{min}^{-1}$ indicate that this anaesthetic technique may be useful to achieve haemodynamic stability. It should be stressed that our data were obtained from ASA I and II patients and we caution against extrapolation of our findings to patients with significant coronary artery and vascular disease. The observation that our technique of intubation had no influence on either cardiovascular responses or the incidence of postoperative sore throat suggests that total i.v. anaesthesia with propofol may be useful for teaching orthodox and fibreoptic intubation skills.

Advancement of the tracheal tube over the fibrescope cannot be controlled visually and injury to sensitive pharyngeal and laryngeal structures may occur. However, there was no difference in the incidence of postoperative sore throat in the two groups. This may have been a result of our emphasis on careful technique rather than speed.

It may be of some potential concern that the airway remained unprotected for significantly longer during fibreoptic than conventional intubation. Silent regurgitation occurs in 4–26 % of patients under general anaesthesia [5], but the clinical significance of this problem is not clear. The patients in this study were at low risk of regurgitation (elective surgery, fasted overnight, competent oesophageal sphincter).

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# RYANODINE CONTRACTURE: A POTENTIALLY SPECIFIC *IN VITRO* DIAGNOSTIC TEST FOR MALIGNANT HYPERTHERMIA

P. M. HOPKINS, F. R. ELLIS AND P. J. HALSALL

## SUMMARY

In vitro *contracture tests used currently for malignant hyperthermia (MH) do not possess absolute specificity. This is potentially a great problem in the study of the genetic approach which offers the best prospect for the development of a non-invasive diagnostic test for the condition. The calcium release channel of the sarcoplasmic reticulum has been proposed as the site of the MH defect. Ryanodine, which binds avidly to this channel, was shown to differentiate between muscle of MH susceptible and normal patients in terms of* in vitro *contracture response. This ryanodine contracture response is proposed as a potentially specific* in vitro *diagnostic test for MH.*

**KEY WORDS**

*Hyperthermia: malignant,* in vitro *test. Pharmacology: ryanodine*

Current methods for diagnosis of malignant hyperthermia (MH) are based upon an abnormal *in vitro* contracture response both to caffeine and to halothane, by muscle taken at open biopsy. The majority of centres screening for MH susceptibility now use either the procedure of the European MH Group [1] or that of the North American equivalent [2].

The halothane contracture test, performed according to the European procedure, is a very sensitive test. The caffeine contracture test appears to produce false negative results in about 15% of MH susceptible patients, but it may provide useful information in subjects in whom the halothane result is borderline. However, both the halothane and the caffeine tests have been shown not to be specific for MH, with positive results occurring in some patients with other muscle diseases known to be genetically distinct from MH [3]. The lack of absolute specificity of the *in vitro* contracture tests for MH is perhaps the greatest hindrance to world-wide efforts to identify the genetic defect in this condition.

Ryanodine, a neutral plant alkaloid, has been shown to cause time- and dose-dependent contractures of normal rabbit and rat skeletal muscle [4]. This is related presumably to its affinity for ryanodine receptor protein, which is now known to incorporate the sarcoplasmic reticulum calcium release channel [5]. This protein, which spans the gap between the terminal cisternae of the sarcoplasmic reticulum and the T-tubule, has been suggested as the site of the MH defect, as [$^3$H]-ryanodine has been shown to have greater affinity for the protein from pigs with porcine stress syndrome than that from normal pigs [6].

Any differences in the contracture response to ryanodine between muscle from MH susceptible and normal individuals may, therefore, form the basis of a test for MH more specific than either the halothane or caffeine contracture tests.

## METHODS AND RESULTS

The muscle specimens used were surplus to diagnostic requirements for patients attending for investigation of MH susceptibility according to the European MH Group procedure. Experiments were performed using muscle fascicles from six MH susceptible (MHS) patients, seven MH negative (MHN) patients and two patients

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TABLE I. *Force of contracture (g) developed in response to incremental doses of ryanodine, caffeine or halothane*

| Patient | Ryanodine concentration (µmol litre$^{-1}$) | | | | Caffeine concentration (mmol litre$^{-1}$) | | Halothane (%) | | |
|---|---|---|---|---|---|---|---|---|---|
| | 0.4 | 0.8 | 1.6 | 10 | 1 | 2 | 0.5 | 1 | 2 |
| MHS 1 | 0 | 0.2 | 0.8 | 1.8 | 0.9 | 2.0 | 0.7 | 2.4 | 4.0 |
| MHS 2 | 0.2 | 0.6 | 1.6 | 3.8 | 0.6 | 0.8 | 1.6 | 2.4 | 2.7 |
| | 0.1 | 0.3 | 1.0 | 2.8 | | | | | |
| MHS 3 | 0 | 0 | 0.2 | 0.8 | 0 | 0.4 | 0.2 | 0.5 | 1.3 |
| MHS 4 | 0 | 0 | 0.2 | 0.6 | 0 | 0.4 | 0 | 0.3 | 1.3 |
| | 0 | 0 | 0.2 | 0.8 | | | | | |
| MHS 5 | 0 | 0.2 | 1.2 | 3.5 | 0.3 | 0.9 | 0.3 | 0.9 | 1.5 |
| MHS 6 | 0 | 0 | 0 | 0.6 | 0.2 | 0.8 | 0 | 0 | 0.6 |
| MHE 1 | 0 | 0 | 0.3 | 1.6 | 0 | 0 | 0 | 0.9 | 2.6 |
| MHE 2 | 0 | 0 | 0 | 0.4 | 0 | 0 | 0 | 0.2 | 1.0 |

whose muscle had an abnormal contracture response to halothane but normal response to caffeine and were therefore classified as MH equivocal (MHE) according to the European procedure. For two MHS and two MHN patients, a second fascicle was available to test for reproducibility.

Immediately after excision, each specimen was placed in Kreb's solution (content (mmol litre$^{-1}$): NaCl 118.1, KCl 3.4, $MgSO_4$ 0.8, $KH_2PO_4$ 1.2, glucose 11.1, $NaHCO_3$ 25.0, $CaCl_2$ 2.5) at room temperature and bubbled with carbogen (95% oxygen–5% carbon dioxide). All experiments were performed within 5 h of biopsy. Muscle fascicles were placed in a muscle bath perfused with Krebs' solution at 37 °C bubbled with carbogen. The muscle was stimulated directly (0.3-Hz, 2-ms square wave) at a supramaximal voltage and the response recorded on a Gould 2200 recorder using an Ormed 4157 force transducer. A baseline tension of 2 g was applied. After 5 min, ryanodine was added incrementally at doses of 0.4, 0.8, 1.6 and 10 µmol litre$^{-1}$, each dose being maintained for 3 min. A contracture was recorded as the increase in baseline tension above the minimum baseline tension. Ryanodine was obtained from Agri Chemicals (Philadelphia, U.S.A.); all other chemicals were obtained from Sigma (Poole, U.K.).

No muscle fascicle from the MHN group of patients developed a contracture in response to the regimen described of exposure to ryanodine. Consequently, the concentration of ryanodine in the muscle bath was maintained at 10 µmol litre$^{-1}$. A contracture response was observed in all samples within a further 12–20 min. In contrast, a contracture developed during the incremental application of ryanodine in all fascicles from MHS patients. The muscle from the two MHE patients behaved in a similar way. Details of the contractures produced are given in table I, with responses to caffeine and to halothane.

The response to ryanodine was compared with those for caffeine and halothane, using Spearman's rank correlation coefficient. Rank order was determined by the threshold concentration for contracture of each drug. Where two or more patients had the same threshold concentration, the size of contracture produced at that concentration was used for ranking. The correlation coefficient for halothane and ryanodine was 0.93 ($P < 0.01$), while that for caffeine and ryanodine was 0.69 ($P < 0.05$).

## COMMENT

This study has demonstrated a method for distinguishing MH susceptible from normal individuals. By studying other members of their families, we have confirmed that the two patients classified as MHE as a result of their halothane and their caffeine contracture tests were indistinguishable from the MHS group using ryanodine as the challenge. This suggests that the ryanodine contracture test is more sensitive than the caffeine contracture test and at least as sensitive as the halothane contracture test. In conjunction with the biochemical abnormality demonstrated on the ryanodine receptor protein in MH pigs by Michelson and colleagues [6], this implies that the ryanodine contracture test may be more specific to MH. The results of this study have important implications for our understanding of the pathophysiology and pharmacology of the ryanodine receptor protein–sarcoplasmic reticulum calcium release channel.

The number of patients involved in this study was small, however, and the results require confirmation. Because of the potential impact of a specific diagnostic test for MH on the analysis of genetic linkage data, laboratories screening for MH susceptibility should consider including a ryanodine contracture test in their procedure.

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# SENSITIVITY, SPECIFICITY AND PREDICTIVE VALUE OF THE SENSATION OF WARMTH AS A METHOD OF DETECTING INADVERTENT SUBARACHNOID INJECTION OF LOCAL ANAESTHETIC WHEN PERFORMING EXTRADURAL BLOCKS

## E. KALSO, U. AROMAA AND T. TAMMISTO

### SUMMARY

*In order to test if the rate of onset of sensation of warmth in the legs after the injection of 0.5% bupivacaine might discriminate between subarachnoid and extradural injection, 150 urological patients were allocated randomly to receive either spinal anaesthesia with isobaric (IS) or hyperbaric (HS) 0.5% bupivacaine, or extradural anaesthesia with isobaric 0.5% bupivacaine. The volume of the local anaesthetic for spinal anaesthesia and for the extradural test dose was 3–4 ml. The patients were asked to report at once if they had a sensation of warmth in the legs during or after injection of local anaesthetic. The mean time to the sensation of warmth was significantly shorter in the spinal groups (80 (*SEM *10) s in IS and 76 (8.0) s in HS) than in the extradural group (558 (38) s). However, six patients in the IS and two in the HS group had no sensation of warmth.*

***KEY WORDS***

*Anaesthetics, local. bupivacaine Anaesthetic techniques: extradural, subarachnoid*

It is generally recommended that a test dose of local anaesthetic is used during performance of extradural anaesthesia, in order to avoid a high spinal block [1]. Lignocaine 2–5 % in a volume of 1.5–2 ml with or without adrenaline is considered to be the most reliable local anaesthetic for use as a test dose [2], whereas isobaric bupivacaine is regarded by some as unsatisfactory because of variability in the level of the subarachnoid block produced and the highly variable onset of action as a spinal anaesthetic agent [3]. The detection of sensory (pinprick) and motor block after intrathecal lignocaine as a test dose involves the inspection, identification and injection of two different solutions and the patient may move during the procedure, thus displacing the Tuohy needle.

In an elegant study, Gordh demonstrated that the first effect of spinal anaesthesia with heavy lignocaine and amethocaine was a subjective feeling of warmth in the feet. This occurred within 30 s after injection of the local anaesthetic and was not associated with sympathetic block [4].

The object of this study was to determine if the sensation of warmth in the lower limbs could serve as a reliable indicator of subarachnoid injection when using 0.5 % bupivacaine as a test dose.

### METHODS AND RESULTS

The study was approved by the Institutional Ethics Committee. After giving informed consent, 150 patients undergoing urological surgery were allocated randomly to three groups of 50 to receive spinal anaesthesia with isobaric (IS) or hyperbaric (HS) 0.5 % bupivacaine, or extradural anaesthesia with 0.5 % isobaric bupivacaine. The spinal or extradural needle was inserted at the 3rd lumbar interspace, with the patient sitting. A dose of bupivacaine 3–4 ml was injected over 20–30 s. The remainder of the extradural dose was injected

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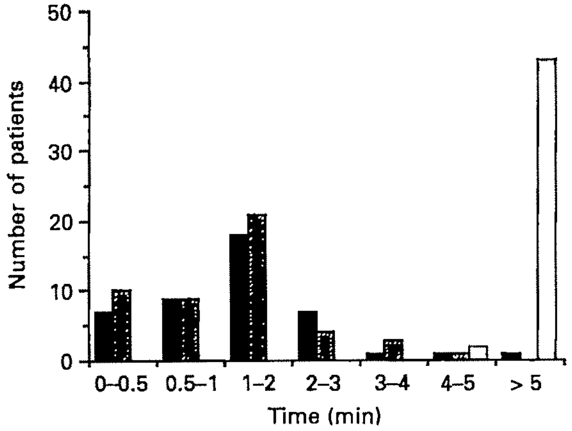

FIG. 1. Numbers of patients experiencing a sensation of warmth in the lower limbs at various times after 3–4 ml of 0.5% hyperbaric (■) or isobaric (▨) bupivacaine injected intrathecally, or 3–4 ml of isobaric bupivacaine as a test dose given extradurally (□) followed by the remainder of the total dose of 16–23 ml after a 3-min interval (50 patients in each group).

after an interval of 3 min. The patient was asked to report immediately any sensation of warmth in the lower extremities. The sensory level (pinprick) and degree of the motor block (Bromage's scale) were noted 20 min after the injection. Mann–Whitney *U* test was used for statistical analysis. Data are reported as mean and SEM.

The patients were comparable in age (mean 69, range 37–89 yr), height (173 (0.6) cm), weight (78 (1) kg) and sex distribution (93% male). The mean time to sensation of warmth was significantly ($P < 0.0001$) shorter in both spinal groups (IS: 80 (10) s; HS: 76 (8.0) s), compared with the extradural group (558 (38) s) (fig. 1). Six patients in the IS, two in the HS and three patients in the extradural group had no sensation of warmth. Fifty percent of those who did not report warmth reported pins and needles or numbness as the first symptom of the block. The groups had comparable sensory block levels (T8 ± 0.2) 20 min after injection of bupivacaine. The frequency of total motor blocks was greatest (78%) in the IS group and least (4%) in the extradural group.

## COMMENT

The sensation of warmth appeared significantly faster in both spinal groups. Only three patients in the isobaric spinal and four in the hyperbaric spinal group reported feeling warmth after 3 min, whereas none of the patients in the extradural group had experienced any sensation of warmth by 3 min. However, six patients in the IS group failed to sense warmth in the lower extremities. One patient in the IS group had severe atherosclerosis, otherwise there were no neurological or other diseases which might have influenced the results. One of the patients described in the study by Gordh [4] had Buerger's disease, but was able to sense warmth in the phantom foot. In that study, only hyperbaric lignocaine and amethocaine were used, which might explain the faster and more consistent appearance of the sensation of warmth. The 88% sensitivity of the test dose in the present study with hyperbaric 0.5% bupivacaine was not significantly better than that (82%) after isobaric 0.5% bupivacaine.

The sensation of warmth in spinal anaesthesia is probably caused predominantly by stimulation of afferent thermal fibres by local anesthetic solution, as the symptom appears much earlier than an increase in skin temperature [4]. In contrast, the late sensation of warmth in the

TABLE I. *Sensitivity, specificity and predictive value of three different test doses at 3 min and 5 min from the injection, assuming that the incidence of dural puncture is 1%*

| | Sensitivity (%) | | Specificity (%) | | Predictive value | |
|---|---|---|---|---|---|---|
| | 3 min | 5 min | 3 min | 5 min | 3 min | 5 min |
| Pinprick analgesia | | | | | | |
| Isobaric 0.5% bupivacaine 1.6 ml [5] | 100 | 95 | 75 | 60 | 0.04 | 0.02 |
| Hyperbaric 1.5% lignocaine 2 ml [2] | 100 | 100 | 99.6 | 75 | 0.72 | 0.04 |
| Pinprick anaesthesia | | | | | | |
| Isobaric 0.5% bupivacaine 1.6 ml [5] | 50 | 70 | 100 | 100 | 1.0 | 1.0 |
| Ability to raise a straight leg | | | | | | |
| Isobaric 0.5% bupivacaine 1.6 ml [5] | 70 | 75 | 100 | 100 | 1.0 | 1.0 |
| Warmth in the legs | | | | | | |
| Isobaric 0.5% bupivacaine 3–4 ml | 82 | 86 | 100 | 90 | 1.0 | 0.18 |

extradural group is more likely to be associated with sympathetic block and concomitant increase in skin temperature.

Prince, Shetty and Miles studied the safety and efficacy of 1.6 ml of isobaric 0.5 % bupivacaine as an extradural test in obstetric patients [5]. They found that complete inability to raise the foot from the bed by hip flexion with the knee held straight was the only definite sign of subarachnoid injection. In addition, the final diagnosis could not be made until 10 min after injection in 10 % of patients. Unfortunately, the sensation of warmth in the feet was not recorded in this study.

If the sensitivities and the specificities of the test doses proposed by Abraham and colleagues [2], Prince, Shetty and Miles [5] and the present study are compared (table I), at 3 min the most sensitive test is pinprick analgesia with plain 0.5 % bupivacaine 1.6 ml and 1.5 % heavy lignocaine 2 ml, the respective specificities being 75 % and 99.6 %. Pinprick anaesthesia and inability to raise a straight leg after plain bupivacaine 1.6 ml and warmth in the legs after 0.5 % isobaric bupivacaine 3–4 ml have 100 % specificity, but the respective sensitivities are 50 %, 70 % and 86 %. Assuming that the incidence of unintentional dural punctures is about 1 % [6], the predictive value of the sensation of warmth and inability to raise a straight leg after 3–4 ml or 1.6 ml, respectively, of 0.5 % isobaric bupivacaine is 1.0, whereas it is only 0.04 if pinprick analgesia is tested after 0.5 % bupivacaine 1.6 ml and 0.72 after 1.5 % heavy lignocaine 2 ml. Prolonging the testing time to 5 min improved the sensitivities of most of the tests, whereas the specificities and predictive values diminished.

It is concluded that the high predictive value of warmth as a method of detecting inadvertent subarachnoid injection compares favourably with other signs, and therefore sensation of warmth after 1.6–2 ml of 0.5 % isobaric bupivacaine as a test dose should be studied in obstetric patients. If it were more sensitive in these patients than in the elderly men in the present study, it would represent a rapid and easy test with a high predictive value. The best follow-up time for a test dose seems to be 3 min, as the predictive value of most of the tests decreases thereafter. In order to improve the sensitivity of a test dose, more than one sign should be sought.

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# NEUROLOGICAL COMPLICATIONS FOLLOWING THE USE OF CONTINUOUS EXTRADURAL ANALGESIA WITH BUPIVACAINE

N. M. DUNNE AND W. J. KOX

## SUMMARY

*We describe a patient in whom continuous extradural analgesia with bupivacaine resulted in toxic plasma concentrations causing severe cerebral irritation. We discuss recent studies using continuous extradural bupivacaine, reports of toxicity and comment on the importance of monitoring drug concentrations.*

### KEY WORDS

*Anaesthetics, local: bupivacaine. Toxicity: local anaesthetics.*

Bupivacaine is an amide-type local anaesthetic drug which causes a greater degree of sensory than motor block [1]. It has been used successfully for intradural [2] and extradural block [3] and also for infiltration [4]. It is no longer used for i.v. regional block because of cardiotoxic effects which occurred after release or failure of the tourniquet [5]. We describe a patient in whom continuous extradural analgesia with bupivacaine resulted in toxic concentrations causing neurological sequelae.

## CASE REPORT

A 57-yr-old man weighing 70 kg was admitted to the Accident and Emergency department following a Road Traffic Accident in which he was the back seat passenger in a car. On arrival, he was fully conscious and responding to commands, but had difficulty in breathing. There was a small laceration and bruising on the left forehead, grazing and bruising over the left anterior chest wall with surgical emphysema and tenderness in the left hypochondrium. X-rays showed fractured ribs 2, 3 and 4 on the left, fractured sternum and fractured mid shaft of left ulna. Because of suspected splenic injury, splenectomy was performed and a left-sided chest drain was inserted. The intraoperative period was uneventful except that oxygen saturation varied between 90% and 92% with an $F_{I_{O_2}}$ of 0.6. This was attributed to the underlying lung contusion.

He underwent elective ventilation of the lungs for 36 h after operation and then sedation was decreased and the trachea was extubated. A few hours after extubation the patient became extremely tachypnoeic, with decreasing arterial oxygen tension in spite of increasing $F_{I_{O_2}}$. This was thought to be caused by inadequate ventilation as a result of pain ($V_T < 250$ ml). The trachea was re-intubated and the lungs ventilated, and a decision was made to insert an extradural catheter to facilitate weaning. A catheter was inserted at T8 using loss of resistance to air to identify the extradural space. An extradural infusion was commenced, using a Vickers Medical Treonic (P3 syringe pump) and a 50-ml syringe containing 0.125% plain bupivacaine, at 6 ml h$^{-1}$ and increasing several hours later to 8 ml h$^{-1}$. After 18 h of infusion, the infusing solution was changed to one of 0.25% and infusion continued with gradually increasing doses to a maximum of 12 ml h$^{-1}$, when pain relief was achieved. Weaning continued throughout this period, but the patient became increasingly agitated and uncooperative, despite maintaining excellent ventilatory effort ($V_T > 400$ ml) and adequate arterial blood-gas tensions. The agitation increased to

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TABLE I. *Plasma concentrations of bupivacaine after discontinuation of extradural bupivacaine infusion. nd = Not detected*

| Time after infusion stopped (h) | Plasma bupivacaine concn (mg litre$^{-1}$) |
|---|---|
| 0 | 4.0 |
| 48 | 0.05 |
| 72 | nd |
| 96 | nd |

such a degree that the patient would no longer obey any commands and it was considered possible that some intracerebral event may have occurred. Cranial computed tomography was performed; this revealed a normal scan.

It was postulated that the agitation may have been caused by bupivacaine toxicity, so the infusion was stopped and the patient given a dose of extradural diamorphine. Venous blood samples were obtained immediately on stopping the infusion and at 48, 72 and 96 h for measurement of plasma concentrations of bupivacaine (table I).

Our patient had received a total of bupivacaine 752 mg over 40 h: approximately 10 mg kg$^{-1}$ over 40 h, or 0.27 mg kg$^{-1}$ h$^{-1}$. No signs of cardiotoxicity were seen at any time. Over the following 72 h the agitation decreased gradually and the patient became more responsive. The following morning he was fully conscious and alert and the trachea was extubated.

## DISCUSSION

Many cases of bupivacaine toxicity have been reported in association with Biers block and it is now common practice to use other local anaesthetics for this technique [5]. The problems associated with bupivacaine ranged from arrhythmias to sudden cardiovascular collapse and cardiac arrest.

Bupivacaine is now used routinely for most extradural blocks because of its duration of action. Studies have shown in orthopaedic [6], obstetric [7] and general surgical patients that continuous infusions of extradural bupivacaine over prolonged periods, with concentrations of 0.0625–0.75 % have not resulted in toxic plasma concentrations. A study by Maier, Wawerski and Wulf [8] of 286 general surgical patients with extradural catheters *in situ* for periods of from 24 h to 45 days and an average daily dose of 75–250 mg resulted in complications in 36 patients: 19 haemodynamic, seven neurological and 10 technical.

Bupivacaine concentrations were assayed using gas chromatography [9]. A comment accompanying the plasma concentrations issued by The Poisons Unit, New Cross, London, stated that values should not exceed 1 mg litre$^{-1}$ and that values in excess of 3 mg litre$^{-1}$ may result in cardiotoxicity and death. There is little information on cerebral side effects. Our patient had a plasma concentration of 4 mg litre$^{-1}$ in the first sample after stopping the infusion. It seems unlikely that altered metabolism of bupivacaine was a problem, as there was rapid clearance when the infusion was stopped.

Although the position of the extradural catheter was not confirmed directly, the improvement in tidal volume following extradural bupivacaine, and subsequently diamorphine, excluded fat or pulmonary embolism as likely causes of the agitation and confirmed indirectly the correct position of the extradural catheter.

We suggest that, when using continuous infusion of extradural bupivacaine, monitoring of plasma concentrations may be necessary if the technique is extended over long periods. The recommended single dose for an adult should not exceed 150 mg and doses of 50 mg 2-hourly may be used subsequently [10].

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# ANAESTHESIA AND CONGENITAL AGRANULOCYTOSIS: INFLUENCE OF ANAESTHETIC AGENT ON NEUTROPHIL NUMBERS IN A PATIENT WITH KOSTMANN'S SYNDROME

S. G. FENNER AND J. N. CASHMAN

## SUMMARY

*We describe a 14-month-old male patient with congenital agranulocytosis who received general anaesthesia on three separate occasions during a 6-week period for minor surgery. Granulocyte colony stimulating factor was commenced after the second anaesthetic. Each anaesthetic was followed by profound reductions in neutrophil numbers, irrespective of the agent used. Even the third anaesthetic, which avoided all the common agents thought to have a marrow suppressant effect and given during granulocyte colony stimulating factor therapy, was associated with a marked decrease in neutrophil numbers.*

**KEY WORDS**

*Anaesthesia: paediatric. Blood: leucocytes, neutrophils. Complications: congenital agranulocytosis.*

Kostmann's syndrome, described by R. Kostmann in 1956, is a rare, autosomal recessive congenital neutropenia [1]. There is usually a history of parental consanguinity. Other congenital abnormalities are commonly associated with this condition [2]. Kostmann's syndrome presents in the first few months of life, with repeated bacterial infections of the skin and respiratory tract. The condition is characterized by the presence of a persistently depressed neutrophil count with variable degrees of thrombocytosis, eosinophilia or monocytosis. The bone marrow from patients with Kostmann's syndrome shows an arrest of myelocyte maturation at the promyelocyte stage. The interaction of anaesthetic agents with neutrophil numbers in Kostmann's syndrome has not been described before. The case presented here describes the effects of three different anaesthetic regimens on the neutrophil count in a child with Kostmann's syndrome.

## CASE REPORT

A 14-month-old Asian male, weighing 9.45 kg, was admitted initially with acute varicella zoster infection and secondary infection of some of the vesicular skin lesions. One lesion in the groin had progressed to a cutaneous abscess. The patient, born of a consanguineous partnership, had a history of recurrent upper and lower respiratory tract infections. At another hospital, this history, together with the results of laboratory investigations, had led to the provisional diagnosis of Kostmann's syndrome [1].

The patient received three anaesthetics during a 44-day period; the first of these, for incision and drainage of the dermal abscess and bone marrow biopsy, was preceded by 3 days of parenteral antibiotics. Before the first anaesthetic, investigations revealed iron-deficiency anaemia (haemoglobin 8.3 g $dl^{-1}$) and neutropenia (leucocyte count $12.7 \times 10^9$ $litre^{-1}$; neutrophil count $0.6 \times 10^9$ $litre^{-1}$). Chest x-ray showed right upper lobe consolidation with partial collapse.

### *First anaesthetic (GA1)*

Premedication with trimeprazine 2 mg $kg^{-1}$ orally was followed by induction of anaesthesia with thiopentone 2.6 mg $kg^{-1}$ i.v. Suxamethonium 1.6 mg $kg^{-1}$ i.v. was given to facilitate tracheal intubation. Anaesthesia was maintained by spontaneous ventilation of 50% nitrous oxide and isoflurane (up to 2%) in oxygen with a fresh gas flow of 7 litre $min^{-1}$ via an Ayres' T-piece with a heat and moisture exchanger. Anaesthesia lasted 35 min and recovery was uneventful. The

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TABLE I. *Haemoglobin, white cell, neutrophil, granulocyte and platelet counts in a patient with Kostmann's syndrome during the period when three different anaesthetics were administered*

| Day | Haemoglobin $(\text{g dl}^{-1})$ | White cells $(\times 10^9\ \text{litre}^{-1})$ | Neutrophils $(\times 10^9\ \text{litre}^{-1})$ | Granulocytes $(\times 10^9\ \text{litre}^{-1})$ | Platelets $(\times 10^9\ \text{litre}^{-1})$ |
|---|---|---|---|---|---|
| 1 | 8.3 | 12.7 | 0.6000 | 0.8540 | 821 |
| 3 | 6.9 | 7.9 | 0.2000 | 0.2000 | 441 |
| 6 | 7.2 | 10.6 | 0.0001 | 1.0600 | 414 |
| 13 | 7.6 | 12.0 | 0.0100 | 0.6120 | 812 |
| 15 | 7.5 | 31.1 | 0.6200 | 1.5530 | 1378 |
| 16 | 8.0 | 15.3 | 0.9000 | 1.5120 | 1060 |
| 17 | 7.8 | 16.2 | 0.3200 | 1.1300 | 1018 |
| 19 | 7.5 | 18.0 | 0.7200 | 1.6200 | 897 |
| 21 | 7.6 | 16.4 | 0.1600 | 0.6520 | 719 |
| 23 | 8.5 | 20.3 | 0.6100 | 0.6100 | 451 |
| 27 | 8.7 | 15.9 | 0.3200 | 0.7970 | 413 |
| 28 | 9.6 | 19.7 | 0.5900 | 0.5900 | 327 |
| 31 | 8.5 | 11.7 | 0.4700 | 0.7040 | 208 |
| 34 | 8.9 | 19.9 | 0.8000 | 2.1930 | 187 |
| 36 | 8.9 | 20.0 | 0.6000 | 1.4000 | 246 |
| 38 | 9.0 | 24.3 | 1.4000 | 1.6430 | 327 |
| 41 | 9.8 | 30.2 | 2.4000 | 3.0040 | 424 |
| 43 | 9.8 | 31.1 | 4.6600 | 6.8370 | 496 |
| 48 | 10.5 | 36.2 | 2.9000 | 5.0720 | 425 |
| 52 | 11.0 | 13.0 | 0.0001 | 0.2600 | 45 |
| 59 | 11.5 | 23.3 | 1.6300 | 2.7950 | 317 |

neutrophil count decreased from $0.6 \times 10^9$ litre$^{-1}$ before this anaesthetic, to less than $1 \times 10^5$ litre$^{-1}$, 4 days later (table I).

*Second anaesthetic (GA2)*

Eight days after the first anaesthetic, anaesthesia was required for rigid bronchoscopy because of persistent right upper lobe collapse. Premedication, consisting of atropine 40 µg kg$^{-1}$ orally, preceded gaseous induction with 50% nitrous oxide and halothane (up to 5%) in oxygen. After induction, nitrous oxide was discontinued because of persistent arterial desaturation associated with an $F\text{I}_{\text{O}_2}$ of less than 1.0. Anaesthesia was maintained with halothane (up to 5%) in oxygen, with spontaneous and manually assisted ventilation using a fresh gas flow of 6 litre min$^{-1}$ via an Ayres' T-piece. Anaesthesia lasted 30 min and recovery was uneventful. The neutrophil count increased from less than $1 \times 10^5$ litre$^{-1}$, 4 days before the second anaesthetic to $0.62 \times 10^9$ litre$^{-1}$, 3 days after it (table I).

*Third anaesthetic (GA3)*

This anaesthetic, 5 weeks after the second, was for a further bone marrow biopsy to assess the effects of the recombinant human granulocyte colony stimulating factor (GCSF) therapy, which had been started after the second anaesthetic. Before operation, it was decided to avoid any anaesthetic agents thought likely to cause bone marrow suppression, in order to maximize the possible benefits which the patient may obtain from the GCSF therapy. After premedication with atropine 20 µg kg$^{-1}$ i.m., anaesthesia was induced with midazolam 100 µg kg$^{-1}$ i.v. and ketamine 2.5 mg kg$^{-1}$ i.v. An additional bolus of ketamine 1 mg kg$^{-1}$ i.v. was required for maintenance. Anaesthesia lasted 25 min and was uneventful. Recovery, in a quiet, well illuminated room, was marked by much more restlessness than had characterized recovery from either of the two previous anaesthetics. The neutrophil count decreased from $4.66 \times 10^9$ litre$^{-1}$ before the third anaesthetic, to $2.9 \times 10^9$ litre$^{-1}$ after 4 days, to less than $1 \times 10^5$ litre$^{-1}$ after 8 days (table I).

The patient had two bone marrow biopsies. The first, at the time of the first anaesthetic before GCSF therapy had been started, showed few neutrophils of a maturation later than that of promyelocyte. The lymphocyte line was normal in number. Monocytes were prominent. These changes were thought consistent with a diagnosis of Kostmann's syndrome with iron deficiency in addition. The second biopsy demonstrated that granulocytes were still markedly reduced, but less so than in the first bone marrow sample and with more at a mature stage. These changes were

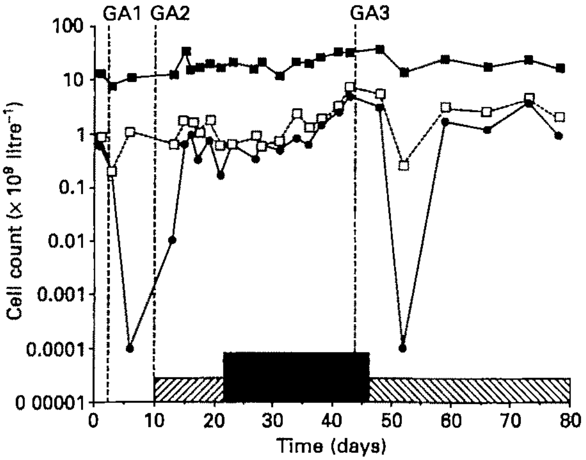

FIG. 1. Total white cell (■), neutrophil (●) and granulocyte (□) counts against time in relation to the three general anaesthetics (GA1–GA3) and GCSF therapy (▨ = 50 μg day$^{-1}$; ■ = 100 μg day$^{-1}$; ▧ = 100 μg every second day).

thought to be consistent with a response to GCSF therapy. Serum vitamin B$_{12}$ and folate concentrations measured on two occasions during this 44-day period were within normal limits. Reticulocyte counts were not performed, even though some of the blood films demonstrated polychromasia. The total white cell, neutrophil and granulocyte counts and their temporal relation to the three anaesthetics over this period are shown in figure 1.

## DISCUSSION

Kostmann's syndrome is characterized by the arrest of neutrophil maturation at the promyelocyte stage [1, 2]. The resultant profound neutropenia leads to an increased susceptibility to and severity of bacterial infections from early infancy onwards. Affected individuals suffer from repeated episodes of infections such as otitis media, skin abscesses, pneumonia and urinary tract infections [1, 2]. These infections progress frequently to systemic illness and septicaemia, hence the serious morbidity and mortality associated with this condition. Management is aimed primarily at prompt treatment of infections [2], including surgical drainage of any abscesses. Bone marrow transplantation has been reported to effect a cure in this syndrome [3]. The beneficial use of recombinant human GCSF in Kostmann's syndrome has been reported [4]. A dose-dependent increase in neutrophil count is seen within 48 h of starting GCSF therapy in normal individuals, although there is a latent period of 8 or 9 days before this increase occurs in patients with Kostmann's syndrome [4]. The increase occurs in a cyclical manner at periods of 7–16 days. This may be the explanation for the dramatic decreases in neutrophil numbers observed over this period in our patient, although we do not believe this to be the case. Apart from the anaesthetics administered over this period, there does not appear to have been any other likely causative agent or incident that would explain these changes.

Following the first anaesthetic (thiopentone, suxamethonium, nitrous oxide and isoflurane in oxygen), neutrophil count decreased to unrecordable values, but with preservation of total leucocyte numbers. Subsequent to the second anaesthetic (nitrous oxide and halothane in oxygen) there was a delayed, moderate increase in neutrophils. However, this observation is complicated by the initiation of GCSF therapy on the day of operation. The dose of GCSF was doubled 22 days before the third anaesthetic, following which there was a rapid increase in the neutrophil count reaching a peak 3 days before the third anaesthetic. This anaesthetic (midazolam, ketamine and oxygen) was followed by a further dramatic reduction in the neutrophil count to unrecordable numbers, accompanied by a marked decrease in total leucocyte count. These reductions in neutrophil and leucocyte counts occurred concurrently with continuing GCSF therapy.

The effects of anaesthetic agents on leucocyte and, in particular, neutrophil function in Kostmann's syndrome have not been described, although there is much information from *in vitro* and *in vivo* studies of neutrophil function and of the complex neuroendocrine effects of surgery and anaesthesia upon this function in humans [5, 6]. The complicating effects of the surgical stress response upon the human immune system, of which the neutrophils form a vital part, make the study of the *in vivo* effects of anaesthetic agents difficult to interpret. Most of the literature deals with *in vitro* experimentation, observing effects on such aspects of neutrophil functioning as chemoluminescence, random and chemotactic migration, phagocytosis and bacterial killing. After surgery there is normally an increase in leucocyte count, mainly as a result of increased neutrophils, despite a decrease in lymphocyte numbers. This increase is evident at the end of surgery and frequently lasts for several days [5–7]. This neutrophilia and some of the adverse effects on leucocytes observed in response to surgery under general anaesthesia may be attenuated by regional anaesthesia [7, 8].

The effects of nitrous oxide on vitamin $B_{12}$, bone marrow and neutrophils have been investigated extensively in the past 30 years. The principal action of nitrous oxide is oxidation of the cobalt moiety of vitamin $B_{12}$. This prevents vitamin $B_{12}$ from functioning as a vital co-enzyme to methionine synthetase, required for tetrahydrofolate and DNA synthesis [8]. As little as 2 h of exposure to anaesthetic concentrations of nitrous oxide may induce megaloblastic marrow changes [9]. The consensus of evidence indicates that short exposures to nitrous oxide in healthy patients have little clinically deleterious effect. However, this cannot be stated with certainty in the case of "sick" patients [10]. The promyelocyte stage is the predominant phase of neutrophil maturation affected by this action [11]. It is of interest that this is the same stage of neutrophil development at which maturation arrest occurs in Kostmann's syndrome [1, 2].

The balance of *in vitro* evidence indicates that, at clinical concentrations, all the inhalation agents in common use (halothane, enflurane and isoflurane) have significant, reversible, depressant effects on neutrophil chemotaxis, phagocytosis and bacterial killing. Isoflurane appears to have the least depressant action of these three agents [8].

The effect of i.v. anaesthetic agents is less well documented. Thiopentone, the i.v. agent studied most, has an inhibitory action on neutrophil action in the concentrations that would be found soon after a bolus dose [7, 12] but, again, not all studies have confirmed this finding. The evidence for other commonly used agents is less definite. Methohexitone probably depresses neutrophil function [7, 12]; benzodiazepines, particularly diazepam, have a slight inhibitory effect [12, 13]; the evidence for significant reversible inhibition of neutrophil function by etomidate is even more equivocal [7]. Ketamine has been found to cause a slight, but significant, inhibition of neutrophil phagocytosis [12] and chemotaxis [13]. However, in both of these studies the concentrations used were greater than those likely to be encountered clinically beyond the initial bolus phase of i.v. dosage, making extrapolation to the *in vivo* situation difficult to interpret. In a study using a clinically relevant concentration of ketamine, Ruud, Benestad and Opdahl found no depression of neutrophil oxygen consumption or coagulation [14]. The authors are unaware of any report of profound neutropenia following ketamine anaesthesia. The neuromuscular blocking agents appear to have no effect [12]. Few of the opioid drugs have been studied; morphine may have a slight inhibitory effect [12], although this is by no means accepted [14].

The first and third anaesthetic techniques used in our patient were associated with dramatic reductions in neutrophil numbers. This is contrary to the usual increase in neutrophil numbers seen in normal individuals undergoing anaesthesia of similar duration. Following the second anaesthetic, there was a relatively small increase in neutrophil numbers, but this was still not to normal values. In addition, this increase was complicated by having occurred after initiation of GCSF therapy which would, itself, be expected to cause an increase in neutrophil numbers.

In conclusion, this report demonstrates that, in the rare cases of congenital agranulocytosis such as Kostmann's syndrome, there is a marked depression of neutrophil numbers associated with minor surgery and anaesthesia using agents with possible bone marrow suppressive effects, such as nitrous oxide. It appears likely that exposure to volatile anaesthetics for a short time may also have adverse effects even when GCSF therapy is administered. Furthermore, the use of ketamine may be associated with detrimental effects on the bone marrow of patients with this condition. It would seem prudent, therefore, to use anaesthetic techniques based on conduction block whenever possible in patients with this type of bone marrow aplasia.

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*British Journal of Anaesthesia* 1991; **66**: 625–626

# CARBOXYHAEMOGLOBINAEMIA AND PULSE OXIMETRY

M. VEGFORS AND C. LENNMARKEN

## SUMMARY

*We compared measurements obtained with a pulse oximeter ($Sp_{O_2}$) against values obtained from a CO-oximeter in a patient with carbon monoxide poisoning. $Sp_{O_2}$ was equal to the sum of the oxyhaemoglobin (HbO) and carboxyhaemoglobin (HbCO) values over the range of HbCO from 30 to 1%. This confirms the experimental findings that pulse oximeters measure HbCO as HbO. The patient was treated with oxygen ($F_{I_{O_2}} = 50\%$) and recovered without any sequelae. Under these circumstances, the half-life of HbCO was approximately 2 h.*

**KEY WORDS**

*Equipment: pulse oximeters. Complications carboxy haemoglobin.*

Pulse oximetry is used widely in emergency situations. The techniques relies on the different absorption of light by oxyhaemoglobin (HbO) and reduced haemoglobin (Hb). At a wavelength of 940 nm, HbO predominates in absorption of light, whereas at 660 nm Hb is the main absorber. Carboxyhaemoglobin (HbCO) also absorbs strongly at 660 nm and, when only two wavelengths are used, is indistinguishable from HbO, as has been confirmed in dogs [1]. We report a case of carbon monoxide poisoning which also confirmed the supposition that pulse oximeters measure HbCO as HbO.

### CASE REPORT

A 26-yr-old man attempted suicide by venting the exhaust of his car into the passenger compartment and subsequently driving the car into a town. He was involved in a traffic accident and brought to the casualty department 15 min later. During the ambulance journey, oxygen ($F_{I_{O_2}}$ approximately 0.5) was delivered at a rate of 5 litre min$^{-1}$ via a Hudson face mask. After the patient was admitted to the hospital, oxygen therapy was continued with 5 litre min$^{-1}$ of oxygen through the same mask. The patient complained of headache and was disorientated, but awake. Initially, he had an arterial pressure of 120/60 mm Hg, heart rate of

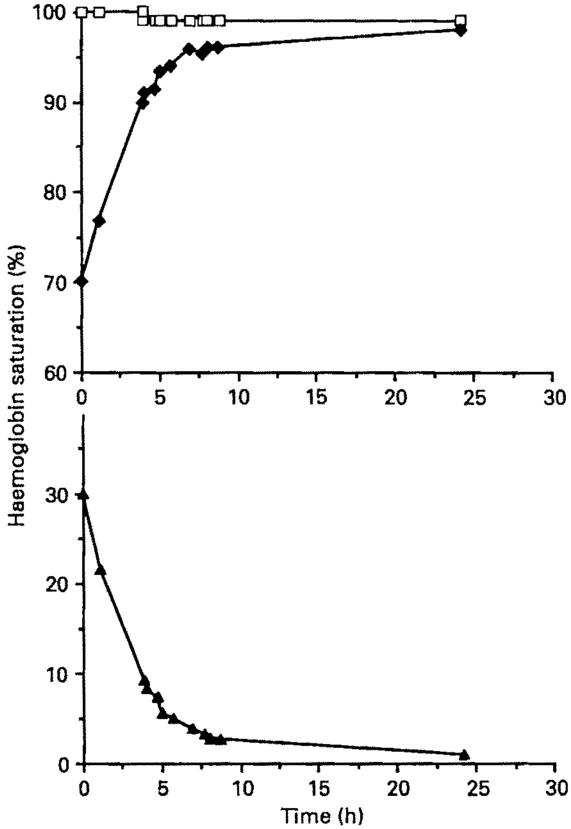

FIG. 1. Changes in saturation of haemoglobin with oxygen (top graph) as measured by pulse oximetry (□) and blood-gas analysis (◆) and with carbon monoxide as measured by blood-gas analysis (▲, lower graph).

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85 beat $min^{-1}$, ventilatory frequency of 18 b.p.m. and the colour of his skin appeared slightly red. At that time, arterial blood-gas analysis showed: pH 7.41, $P_{CO_2}$ 5.39 kPa, $P_{O_2}$ 37.4 kPa, base excess 1.5 mmol $litre^{-1}$, standard bicarbonate 26.1 mmol $litre^{-1}$ (ABL-3, A/S, Copenhagen, Denmark), HbO 70% and HbCO 30% (OSM-3, A/S, Copenhagen, Denmark). A pulse oximeter probe was placed on the finger (Satelite trans, Datex Instrumentation Corp., Helsinki, Finland) and displayed $Sp_{O_2}$ 100%. The values returned to normal in approximately 24 h (fig. 1). The difference between (HbO+HbCO) and $Sp_{O_2}$ was mean 0.2 (SD 0.5)% throughout the period of observation; $Pa_{CO_2}$ remained normal, without acidosis, throughout. The patient recovered without sequelae.

## DISCUSSION

This report confirms that pulse oximetry may be misleading during carbon monoxide poisoning as the pulse oximeter does not differentiate between HbO and HbCO. Diagnosis of carbon monoxide poisoning therefore relies on clinical evidence and must be confirmed by measuring the HbCO concentration with a multiple band CO-oximeter.

Oxygen competes with carbon monoxide for the same sites on the Hb molecule. HbCO concentration greater than about 20% usually indicates poisoning, and requires treatment with oxygen to accelerate the dissociation of HbCO. At an HbCO concentration greater than 40%, there is a risk of neurological damage such as ataxia or cortical blindness and HbCO concentrations in excess of 50% may produce severe, irreversible CNS damage. Patients who manifest signs of serious intoxication, for example unconsciousness or altered neurological function, should be considered candidates for hyperbaric oxygen therapy [2].

Adult blood usually contains four species of haemoglobin: oxyhaemoglobin (HbO), reduced haemoglobin (Hb), methaemoglobin (MetHb) and carboxyhaemoglobin (HbCO). Being two-wavelength devices, pulse oximeters can differentiate only two species of haemoglobin. At 940 nm, HbCO absorbs very little light, but at 660 nm it absorbs as much light as HbO [3]. HbCO is therefore registered by the pulse oximeter as HbO [3]. Barker and Tremper [1] confirmed this in dogs.

The elimination half-life of HbCO is approximately 5 h when air is inspired and 1 h when 100% oxygen is administered at ambient pressure [4]. The half-life of HbCO in our patient was about 2 h, suggesting that the $F_{I_{O_2}}$ was sufficient. During hyperbaric treatment supplied at 3 ata, the half-life of HbCO is reduced to approximately 20 min [5].

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*British Journal of Anaesthesia* 1991; **66**: 627–631

# CORRESPONDENCE

## THE HERING–BREUER REFLEX IN MAN?

Sir,—In a recent Postgraduate Educational Issue of the journal, Dr Nunn stated that the Hering–Breuer reflex is virtually non-existent in man [1]. On the contrary: this reflex has been demonstrated in humans anaesthetized with halothane [2] or Althesin [3], in addition to its existence in anaesthetized animals. It is regrettable that as eminent a physician as Dr Nunn failed to mention this, even if the exact role of this reflex is unclear.

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Sir,—I am indebted to Dr Gaudy for drawing my attention to his studies in anaesthetized man. In one of these, end-inspiratory occlusion resulted in a 10% prolongation of the following expiration in eight of nine subjects [1]. After end-inspiratory occlusion, lung inflation of 250 ml caused a 40% slowing of breathing (which did not appear significant). Larger inflations caused significant slowing of breathing up to 15-fold at 1 litre (equivalent to an inflation pressure of about 20 cm $H_2O$). It is not in doubt that the Hering–Breuer reflex can be detected in man, but the question at issue is whether or not it is of any practical relevance to the control of breathing in man, as it is in most laboratory animals.

A letter does not allow adequate space to debate the validity of my statement that the Hering–Breuer reflex is virtually non-existent in man. However, perhaps I may be permitted to draw attention to the five most important observations on which my opinion is based.

(1) From the comparative study of Widdicombe [2], I would cite figure 1, reproduced here, which speaks for itself. Widdicombe concluded that "... caution must be exercised before ascribing any important role to the Hering–Breuer reflexes in modifying the pattern of breathing in healthy man."

(2) Bilateral vagal block in man causes no detectable changes in the pattern of breathing (in contrast to the slowing which occurs in a range of laboratory animals) [3].

(3) Human heart–lung transplant (with loss of baroreceptor output from the lungs) does not change ventilatory frequency or its components [4].

(4) Every anaesthetist will have observed that, in gross bradypnoea (e.g. after opioids), a brief lung inflation often triggers inspiration.

(5) End-expiratory obstruction (effectively, lung inflation) *augments* the inspiratory force developed by the diaphragm [5]. This augmentation resulted in a further increase in lung volume in all patients up to 6 cm $H_2O$, in 75% of patients in the range 7–9 cm $H_2O$, and in 8% of patients in the range 10–16 cm $H_2O$.

The recorded observations in the last study do not exclude the possibility that expiration was prolonged slightly by expiratory occlusion, but I quote from the first paper cited by Dr Gaudy [6]: "La trachée est occlue en fin d'inspiration ou d'expiration spontanée (Head, 1889) sans aucune réponse du type Hering–Breuer." The feature of practical importance is that inspiratory effort is *stimulated* by moderate inflation of the lung in anaesthetized man, which is quite contrary to what might be expected from an uncritical extrapolation of Breuer

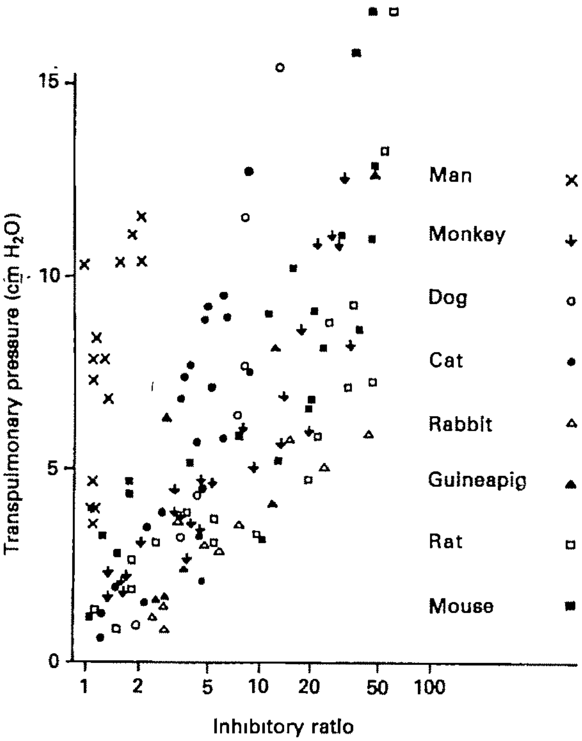

FIG. 1. The Hering–Breuer reflex in different species: ratio of apnoea during inflation to the duration of the previous ventilatory cycles (abscissa) as a function of the increase in transpulmonary pressure causing inflation of the lungs (ordinate). (Reproduced from Widdicombe [2] with permission of the author, and the editor and publishers of *Clinical Science*.)

and Hering's observations in animals. Many new graduates do not appreciate that the Hering–Breuer reflex is not a major factor in control of ventilatory movements in man, as it is in so many laboratory animals.

J. F. Nunn
*London*

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## OXYGEN CYLINDERS ON ANAESTHESIA MACHINES

Sir,—The case report by Jawan and Lee [1] illustrates that there is always a possibility of administering the incorrect gas to a patient instead of oxygen, and they make two recommendations which should be mandatory to prevent future mishaps: first, increased vigilance is required on the part of anaesthetists and theatre staff in checking cylinders; second, there is a need to monitor the inspired oxygen concentration with an oxygen analyser, and oxygenation of the patient with a pulse oximeter.

However, they omitted a third recommendation concerning the number of oxygen cylinders which the anaesthetic machine should carry. It appears obvious from the case report that the anaesthetic machine used by the staff had only one oxygen cylinder, either because the machine had one cylinder only, without a spare oxygen cylinder on the second oxygen port, or because they may have used a newer anaesthetic machine with provision for only one oxygen cylinder (Ohmeda Excel 210), unlike other models which carry two oxygen cylinders in addition to the oxygen pipeline supply (Boyle Major). The recommendation in the former case is to have a second full oxygen cylinder available on the machine at all times. In the latter instance, a strong recommendation must be made to manufacturers that anaesthetic machines should have provision for two oxygen cylinders in addition to the oxygen pipeline supply.

In the absence of a pipeline supply (as in the authors' case) or during a prolonged failure in the oxygen pipeline supply during anaesthesia, the hurried replacement of an empty cylinder by a full cylinder could be difficult and dangerous. As demonstrated by the case report, the change of cylinders under the circumstances described may have contributed to the delay in recognizing the markings on the cylinder. For some reason, this safety feature of older anaesthetic machines has been discontinued on newer versions. In our opinion, this is unquestionably a retrograde step for the safety of modern anaesthesia. The provision of two oxygen cylinders in addition to the oxygen pipeline supply on anaesthetic machines must be included in the minimum standards of requirements for those machines, and in the minimum standards of monitoring during anaesthesia and recovery [2] in order to prevent future mishaps.

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H. S. L. Moseley
A. Y. Kumar
*Barbados*

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Sir,—We agree fully with the opinion of Drs Shankar, Moseley and Kumar that more than one oxygen cylinder should perhaps have been available on our anaesthesia machine. The anaesthesia machine used in the Radiology Department was a Narkomed (North American Dräger) and has two yokes for oxygen cylinders. However, as Shankar and colleagues pointed out, in modern hospitals where piped-in oxygen is a routine, we become more lax as to the availability of supplementary oxygen. In our opinion, it should be made mandatory that in places where piped-in oxygen is not available, two oxygen cylinders should be attached to the anaesthesia machine, while in rooms where piped-in oxygen is a routine provision, at least one oxygen cylinder should be available.

B. Jawan
J. H. Lee
*Kaohsinang Hsien, Taiwan*

## EXTRADURAL OPIOIDS

Sir,—I read with interest the recent correspondence from Nagle and McQuay [1] on extradural pethidine. They suggested that its rapid onset resulted from systemic uptake rather than a spinal effect following dural transfer. In support of this, they made several assumptions on the potency of pethidine and its ability to penetrate the dura.

Several studies have shown a rapid onset of analgesia after extradural pethidine, and a high CSF:plasma concentration ratio exceeding 70 at 5 min [2] supports a predominantly spinal action. Systemically absorbed pethidine may contribute to the effect, but plasma concentrations of pethidine following extradural administration have been demonstrated to decrease to less than minimal analgesic blood concentrations before analgesia ceases [3].

With respect to fentanyl, Nagle and McQuay claimed that doses of 1–5 mg were necessary for spinal action; this represents a dose of 5 to 50 times that used commonly in clinical practice. The use of such large doses would invariably result in respiratory depression. Loper's recent study, which compared i.v. and extradural infusions of fentanyl after knee surgery [4], was quoted to support a systemic rather than a spinal site of action. With extradural infusions, both pharmacokinetic and pharmacodynamic assessments are difficult. Dural penetration, fat deposition and systemic absorption play a role, and sustained blood concentrations also contribute to analgesia. That this study demonstrated similar plasma fentanyl concentrations after i.v. and extradural infusion measured at 18 h does not imply that the site of action of fentanyl is systemic, only that there is no clinical benefit from extradural fentanyl at these doses. Analgesia in both groups was good. The infusion rate of $100\ \mu g\ h^{-1}$ was relatively high: $60\ \mu g\ h^{-1}$ has been shown to be the optimum rate of infusion after thoracic surgery [5]. It may be that fentanyl has a narrow therapeutic window, with high extradural infusion rates producing a high incidence of side effects without improved analgesia. A smaller dose, perhaps optimized to each patient, may well produce "selective spinal analgesia" with fewer side effects than result from an equianalgesic dose administered i.v.

Extradural pethidine has been shown to be more effective than i.m. injection in the treatment of post-Caesarean section pain [6] via action at a spinal level. Pharmacological targeting of the dorsal horn of the spinal cord with both opioid and non-opioid agents potentially offers opportunities for more effective treatment of postoperative pain and should not be dismissed as an exotic alternative to i.m. injection.

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Sir—Thank you for the opportunity to reply to Dr Smart. The letter highlights the widespread confusion that exists in understanding the relationships between plasma or CSF concentration and analgesic effect. The potency ratio for two drugs given systemically is not the same as the potency ratio for the same drugs acting spinally. It should not come as a great surprise to learn that the relative efficacy of different drugs changes with spinal administration. If the pharmacokinetics/dynamics were the same for the two routes, there would be little possibility of achieving better analgesia with spinal rather than systemic administration for any of the opioids. Large (or small) concentrations of a drug in either plasma or CSF do not guarantee better (or worse) analgesia than the drug with which it is being compared; we need to know the potency ratio for that drug and that route of administration. This is precisely the point we were trying to make.

The animal studies quoted by us [1, 2] measured electrophysiologically the antinociceptive effects of various opioids in the spinal cord, and tell us their relative potency. These results suggest that the potency of morphine applied directly to the spinal cord is much greater, relative to the more lipophilic drugs, than the systemic potency ratios with which all anaesthetists are familiar. Systemic morphine 10 mg gives the same antinociceptive effect as fentanyl 0.1 mg (a systemic potency ratio of 1:100) but intrathecally, morphine 1 mg has the same antinociceptive effect as fentanyl 2–10 mg (an intrathecal potency ratio of between 1:0.5 and 1:0.1). We certainly agree with Dr Smart that such an intrathecal dose of fentanyl would produce severe side effects such as respiratory depression. However, the rapid onset of this effect (within minutes) [3] suggests that it is systemically mediated and not related to the high CSF concentration.

The animal evidence is supported by the finding in clinical practice that intrathecal methadone 20 mg failed to produce analgesia of the same duration as intrathecal morphine 0.5 mg [3]. The intrathecal potency ratio is, therefore, not the same as the systemic potency ratio, which is 1:1 for single doses of methadone and morphine. CSF concentrations of methadone would presumably have been very great in these patients, but the analgesic effect was unimpressive. Side effects were more impressive. The study had to be terminated because three of eight patients receiving intrathecal methadone 20 mg became apnoeic.

When dealing with the extradural route, the barrier of the dura mater must also be considered. Thus little clinical advantage would be expected with extradural use of lipophilic opioids compared with the same dose given systemically. This is precisely what has been shown by Loper and colleagues [4] and more recently by Ellis, Millar and Reisner [5]. Dr Smart argues that similar plasma concentrations after either systemic or extradural fentanyl, associated with a similar degree of analgesia (in the paper by Loper and colleagues) do not tell us that the site of action of fentanyl was systemic. This statement is true, but the facts suggest that the sites of action were the same and proved no clinical advantage from extradural fentanyl. Why, then, give the drug extradurally rather than systemically? Use of the extradural route necessarily increases morbidity. We must be certain there is the potential for gain before we subject patients to the "extra" risk.

Measurements of plasma or CSF concentration without reference to effect may be misleading; high CSF concentrations of lipophilic opioids (whether from large or small doses) do not guarantee any improved effect over the same dose given systemically. If extradural opioids are used in combination with local anaesthetic there may be synergy, and the overall result may be better than that of either constituent alone [6]. The details of the pharmacology and physiology of this interaction are unresolved. We agree with Dr Smart that pharmacological targeting of the dorsal horn cells may offer improved treatment. However, using a pharmacological weapon because it happens to be available and placing it in the general vicinity of the spinal cord does not guarantee either that the target will be hit or that the desired result will follow!

H. J. McQuay
C. J. Nagle
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## HIGH FREQUENCY VENTILATION

Sir,—We congratulate Dr Smith on his excellent review article "High frequency ventilation: past, present and future" [1] and wish to comment on external high frequency ventilation, which was not mentioned.

External high frequency ventilation may be achieved by oscillating either the chest wall (high frequency chest wall oscillation (HFCWO)), or the entire body surface (high frequency body surface oscillation). The latter technique is able to maintain adequate ventilation in small animals [2] but, as yet, not in large animals or humans. HFCWO has been shown to produce adequate ventilation in anaesthetized dogs, using a modified arterial pressure cuff to compress the chest, and a reciprocating pump [3]. In conscious man, this technique is sufficient only to assist ventilation, and causes a reduction in functional residual capacity [4]. These problems may be overcome by applying an oscillating pressure to a cuirass, and in order to prevent lung collapse the oscillating pressure is superimposed on a negative baseline. This technique has been successful in cats with normal and stiff lungs [5].

The Hayek Oscillator (Breasy Medical Equipment Ltd, London) is a device which has been developed for use in humans. It consists of a lightweight flexible cuirass connected to a high frequency oscillator which oscillates the chest about a variable negative pressure, allowing control over end-expiratory lung volume. Using the Hayek Oscillator, four children with various lung diseases have been managed [6] and two children after total cavopulmonary anastomosis have shown improved pulmonary blood flow [7]. We have achieved successful ventilation in six normal adult subjects using the Hayek Oscillator, with no untoward effects [unpublished observations].

We believe the use of HFCWO in patients with respiratory failure may have distinct advantages over other modes of ventilation, avoiding both the need for tracheal intubation and the risk of barotrauma; improving inspiratory muscle function [8], and as a technique for weaning and improving tracheal mucus clearance [9]. It may have a significant impact in the physiotherapy and care of ambulatory patients with chronic bronchitis [10]. The early problems have now been overcome by the development of the first practicable oscillating system, the Hayek Oscillator, and we are conducting further studies to determine its clinical role.

V. S. Sidhu
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Sir,—Thank you for the opportunity to reply to the letter from Drs Sidhu, Cummin and Al-Saady.

The purpose of my article was to present some of the newer modes of ventilatory support which have undergone adequate clinical trial and which may or may not have found a clinical role. In this context the techniques of high frequency chest wall oscillation and high frequency body surface oscillation, interesting though they may be, have not, to my mind, been investigated sufficiently. At the time of writing, the techniques had been used only in animals and to my knowledge had not been used in any other than those with normal lungs. Therefore, I felt that it would be premature to include a review of these techniques in such an article.

B. E. Smith
*Redditch*

## DEXTRAN PRELOADING BEFORE EXTRADURAL BLOCK

Sir,—I was interested to read the paper by Drs Wennberg, Frid, Haljamae, Wennergren and Kjellmer [1] comparing Dextran 70 and Ringer's acetate for preloading in extradural Caesarean section. In this study, women receiving crystalloid preloading had a lower mean arterial pressure in the first 30 min after extradural block. Measured changes in thoracic impedance suggested an increase in interstitial lung water in this group. These changes induced the authors to suggest that colloid solutions may be preferable for preloading.

I found this assertion worrying. It is probably true that colloid preloading is associated with greater cardiovascular stability, but the supposed benefits are entirely theoretical as there was no demonstrable improvement in outcome for mother or baby. On the other hand, colloid solutions may cause fatal hypersensitivity reactions. Improvements in gelatine technology and the introduction of Dextran 1 have improved safety, but saline solutions are safer because they do not cause hypersensitivity reactions. If any agent is brought into regular use, its side effects cease to be rare and any maternal death caused by this mechanism would have been an avoidable tragedy.

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*Cardiff*

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Sir,—Thank you for the opportunity to respond to the comments of Dr Slade. We agree that the risk of hypersensitivity reactions to dextran solutions, although minimal when using Dextran 1, is of concern. Maternal hypotension resulting in a decrease in uteroplacental blood flow, on the other hand, is also a risk factor and there is a need for efficient volume loading and prompt administration of i.v. ephedrine [1]. Marx, Cosmi and Wollman [2] demonstrated in 1969 that expansion of intravascular volume was a prerequisite to the effectiveness of ephedrine in correcting maternal hypotension. In most studies, including the present one, colloid solutions have been shown to be more efficient.

None of the colloids available is devoid of the risk of untoward effects, not even natural colloids. According to some data [3] the frequency of morbidity from starch or albumin solutions exceeds that of dextrans. In addition, the increased viscosity of pregnancy [4] should be considered, as pulmonary embolism is reported to be the leading cause of maternal death [5]. In this respect it is well known that dextran is effective in reducing blood viscosity.

When administration of dextran (40, 60 or 70) is preceded by i.v. administration of 20 ml of hapten-dextran (Dextran 1), the incidence of infrequent reactions to the presence of dextran-reactive antibodies is reduced by antibody inhibition. The risk of maternal death after dextran infusion after hapten pretreatment is therefore extremely small. However, during the past year or two a few cases of adverse drug reactions have been reported, consisting of relatively mild anaphylactoid reactions in women during labour leading to severe fetal reactions and even to mortality. In none of the cases known to us was correct hapten pretreatment given. Because a causal relationship may exist between administration of dextran and fetal reactions, it follows that dextran should never be infused without correct hapten pretreatment. The decision to administer dextran should also include, of course, a strict assessment of the medical indication for the use of colloid; it should be remembered that the risk of anaphylactoid reactions is even greater when other colloids (starch, gelatin, albumin) are chosen [3, 6].

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*Gothenburg*

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# BOOK REVIEWS

*Spinal Cord Injuries. Anaesthetic and Associated Care*, 1st Edn. Edited by J. D. Alderson and E. A. M. Frost. Published (1990) by Butterworths, London. Pp. 258; indexed; illustrated. Price £50.00.

The Editors of this book emanate from Sheffield, U.K., and New York, U.S.A., and they have gathered a team of 15 authors who originate largely, but not exclusively, from these two centres; this adds to the interest of the book, as similarities and comparisons may be made in treatment and outcome.

The book gives a very full account and review of all aspects of the treatment of patients who have sustained a spinal cord injury. After an initial chapter dealing with the pathophysiology of spinal cord injury, the subsequent chapters go on to consider the acute care of the spinal cord injured patient, from the scene of the accident, to the resuscitation room in hospital, the anaesthetic management for emergency surgery, and management in the intensive care unit. This is followed by a chapter dealing with aspects of the chronic care of these patients. To complete the text, there are chapters dealing with management of the chronic pain which these patients suffer, current trends in research, and moral and legal issues in the treatment of these patients. There is also a very useful chapter dealing with aspects of anaesthesia for non-traumatic spinal disease. The topic in each chapter is thoroughly discussed, and well referenced, but as with all multi-authored texts, the standard does vary from chapter to chapter.

In summary, this book gives a very thorough review of all aspects of the management of patients who have sustained a spinal cord injury, and should be of interest to all anaesthetists involved in their management, in either the acute or chronic phases. It should also prove very useful reading for candidates preparing for the final part of the Fellowship examination.

*J. L. Jenkinson*

*The Year Book of Critical Care Medicine*, 8th Edn. Edited by M. C. Rogers and J. E. Parrillo. Published (1990) by Year Book Medical Publishers Inc., Chicago. Pp. 310; indexed. Price £34.00.

The *Year Book* series will be familiar to many anaesthetists. The format of summaries of selected papers from a large number of, predominantly American, journals together with editorial comments, is common to the series and it is intended that the book acts as an annual literature review.

The *Year Book* is divided into 10 chapters covering most aspects of critical care medicine. Previous editions have failed to cover the full range of conditions encountered in critically ill patients by concentrating excessively on cardiorespiratory disease—a deficiency which has been addressed in this edition. The book is well indexed by both author and subject and is up to date, including papers published up to July 1989.

This series of books has some disadvantages. A reliance is placed upon the editors in selecting suitable papers and the summaries are often too brief to allow an assessment of the scientific content of the work undertaken. Some of the editorial comments are idiosyncratic, reflecting the personal prejudices of the editor concerned, but this is usually obvious and, to some extent, makes the book more readable and enjoyable. A chapter on socio-economic and ethical issues is included, and it is clear from this and other chapters that the practice of Intensive Care medicine across the Atlantic is ever more similar to that in the U.K.—or is it *vice versa*?

The *Year Book* is not comprehensive, and those with a special interest in this field might do better to keep an eye on the major source journals for themselves. It is difficult to recommend it for individual purchase, but the book does succeed, to a large extent, in its review function and might usefully find a place in the hospital or departmental library, to dip into or to act as a source of references.

*G. Routh*

*Problems in Respiratory Care: The Respiratory Muscles.* Edited by M. J. Tobin. Published by J. B. Lippincott Company, Philadelphia. Pp. 542; indexed; illustrated. Price $60.

Thirty years have passed since Moran Campbell's monograph on the respiratory muscles opened the floodgate of scientific research on the subject. The acquisition of knowledge in this area over the past decade has been matched only by the number of review articles and weighty volumes, many of which have been produced with more enthusiasm than objectivity. Recently, the atmosphere has become more reflective and a sense of perspective has now appeared. The editor of this book makes an apparently presumptive comparison to the classical monograph by suggesting that it covers the clinically relevant topics that should have appeared had the knowledge been available at the time. This is not necessarily an empty claim, and the book has much to recommend it.

The 16 chapters review different aspects of the respiratory muscles. The chapter authors are acknowledged experts in the field from both sides of the Atlantic, but do not hold partisan views about their particular chapter subject. The result is a compilation which is authoritative, balanced and up-to-date. The style is readable, with explanations rather than equations, and each chapter contains at least one summary of its contents.

The subjects which are covered include the structure and physiology of the respiratory muscles, functional measurement and the effect of fatigue, nutrition and pharmacology. Further chapters are devoted to specific diseases, weaning from ventilation and rehabilitation, training and rest. The editor apologizes for overlap of material between chapters, but this is not obvious and each is thoroughly referenced. The chapters on fatigue and pharmacology are both commendably restrained in their coverage of subjects which have previously been exposed to hyperbole.

Some criticism of the book can be directed towards its balance. There is, for example, an exceedingly long chapter on the electrical activation of the diaphragm. The distinction between rehabilitation and respiratory muscle training also seems a little blurred and artificial. The major defect, however, is the book's scanty coverage of mechanical support for patients with ventilator pump failure. This is a growing and productive area that warrants more than a few paragraphs at the end of the book.

It is therefore not quite a perfect book, but does have many excellent features which would be of reference value to anyone with an interest in the subject. Since it is relatively inexpensive by modern standards, it should appeal to intensive care physicians and any anaesthetists with an ambition to widen their knowledge.

*M. D. L. Morgan*

*Studies of Narcosis*. By Charles Ernest Overton, 1st Edn. Edited by R. L. Lipnick. Published (1991) by Chapman and Hall and Wood Library Museum of Anesthesiology, London, Chicago. Pp. 203; indexed; illustrated. Price £35.00.

This is the first translation into any language of Overton's pivotal description of chemical structure, cell permeability and a possible mechanism of action of anaesthetic agents. It was published originally as *Studien uber die Narkose* in 1901, at the same time as Meyer's independent research concluded that anaesthetic potency correlated with partition coefficient.

There is a brief foreword by the editor which explains his personal interest in Overton's work and how he was able to facilitate the production of the book with the help of the Wood Library Museum of Anesthesiology in Chicago and also after considerable assistance from Overton's family.

Two introductions follow this. The first, by Keith Miller, places Overton's research in a historical framework, discussing contributions by Schleiden and Schwann on cell structure in the late 1830s and Quincke's and Pfeffer's work on cell membranes in the 1880s and 90s, respectively. He claims Overton's two main contributions to science are his two rules—the Overton permeability rule and the Meyer–Overton rule of general anaesthesia.

The second introduction, by Winler and Firestone from Pittsburgh, provides a few biographical details and an explanation of the early development of anaesthetic drugs which were used without any understanding of their mechanism of action. They highlight Overton's concepts as intuitively brilliant, considering the lack of apparatus available to him with which to explore the cell membrane. He was nevertheless able to postulate a very accurate theoretical model which was valid for the inhalation agents of that time and for the future. He also understood that different drugs acted in different ways—that is, that the opioids differed from the inhalation agents.

In the third chapter, the editor reprints his paper of 1986, from *Trends in Pharmacological Sciences*, which reviewed Overton's basic work and its contribution to basic understanding of the pharmacology of narcosis and anaesthesia. He highlights Overton's importance to toxicologists with his explanation of structure–toxicology relationships.

Overton's work is then presented. His monograph is in nine chapters, divided into two sections. It starts with a preface in which he pays tribute to Professor Meyer of Marburg, whose name is now linked with Overton. Both had arrived independently at similar conclusions on a theory of narcosis, Overton admitting that his was derived whilst pursuing a study on osmosis in plant and animal cells.

The first section is entitled a general section, and the first chapter deals with the background to Overton's theories, including the factors to be considered by a theory of narcosis and the work of Claude Bernard, Dubois and Bert. He reviews how drugs may be classified into three groups by considering their ability to pass by osmosis through a cell membrane composed of lecithin and cholesterol.

The second chapter reviews critically previous theories of narcosis, including the work of Claude Bernard, Binz, Dubois, Bibra and Harless and Hermann. It is interesting to note that Bibra and Harless had produced, as early as 1847, a theory which correlated anaesthetic potency with ability to dissolve fats. The third chapter elaborates Overton's (and Meyer's) lipoid theory of narcosis relating to partition coefficients.

The second section comprises experimental data presented in six chapters. He deals in turn with narcosis induced by ether and chloroform, aliphatic non-electrolyte organic compounds and narcosis, aromatic compounds, inorganic anaesthetics and basic narcotics and basic compounds. A whole series of tadpoles, crustaceans and other organisms were immersed in a wide variety of chemicals, some of which are anaesthetically relevant (such as ethyl chloride, alcohol, chloral hydrate, eugenol, thymol, carbon dioxide and nitrous oxide) while others are less relevant (such as turpentine, phenol, tartaric acid and citric acid).

In addition, there are three Appendices: the first deals with detoxification by dialysis, the second lists Overton's publications and the last details publications about Overton and analyses of his data.

This book will not be purchased by every anaesthetist. It will (and should) sit on the majority of departmental library shelves where it will allow (for the first time) the anaesthetist who is not familiar with the German language to read the foundations of the Meyer–Overton theory of narcosis. This lipoid theory is cited by multiple authors and still remains a basic tenet of mechanisms of anaesthetic action. The Wood Library Museum of Anesthesiology and the editor, Robert Lipnick, have furnished a great benefit to our specialty by the translation and publication of this excellent book. Had I not been asked to review this book, it is likely that I would have passed it by on the shelves of a bookshop or library, being deterred by its title and its esoteric scientific nature! This would have been to my considerable loss and I would urge other anaesthetists not to make a similar error, but to read it. They will be pleasantly surprised.

*D. J. Wilkinson*

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*"I would have everie man write what he knowes and no more."*—MONTAIGNE

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# EDITORIAL

## CONSCIOUS AWARENESS DURING GENERAL ANAESTHESIA—WHAT ARE WE ATTEMPTING TO MONITOR?

Although it is more than 150 years since general anaesthesia was introduced we still cannot connect a paralysed patient to a monitor to indicate whether or not s/he is in a state of anaesthesia. There are many monitoring methods that have been advocated and these have been reviewed extensively elsewhere [1]. They may be classified into two distinct groups: those that attempt to detect conscious awareness directly and those indirect methods which are, essentially, bioassays of anaesthetic depth. The classical example of a direct method is the Isolated Forearm Technique [2]: one forearm is protected from neuromuscular block with a tourniquet and, at intervals, the patient is asked to squeeze the anaesthetist's hand in a specified way. This has practical problems; first, the patient's arm is free to interfere with surgery should the anaesthetic be light enough for spinal reflexes to be preserved; second, there are documented incidences of false negatives, that is, when the patient was awake but unable to obey commands [3]; third, it is impossible to quantify the false positive and false negative rate after operation because of the powerful amnesic properties of anaesthetic drugs. Nevertheless, the Isolated Forearm Technique is an attempt to deal with conscious awareness itself. Virtually all the other methods proposed are bioassays of anaesthetic depth and therefore have one major problem in common—a leap has to be made from the patient's responses with these various methods to deciding whether or not the patient is asleep. With all its problems, the Isolated Forearm Technique is the nearest we have to a "gold standard" against which to evaluate these methods, so it is not surprising that it is difficult to standardize such indirect variables as autonomic signs [3, 4], lower oesophageal contractility [5, 6], EEG frequency [7] or the latency and amplitude of evoked potentials [8] such that, beyond a certain response, one can be sure that the patient is not in a state of conscious awareness.

Of all these variables, the latency and amplitude of the early cortical auditory evoked potentials [9–15] seems to be the most promising, and these waves, with latencies of about 50 ms, provide direct evidence of one aspect of cortical function. However, Libet and colleagues [16–18] showed that an early cortical evoked potential may occur in the absence of any conscious awareness of the eliciting stimulus and, when conscious awareness does occur, it does so up to 500 ms after the stimulus. This concept is critical to the understanding of conscious awareness, but the work of Libet and his colleagues is not known widely in anaesthetic circles. It will, therefore, be reviewed briefly here.

During the 1960s and '70s, a range of neurosurgical procedures were being undertaken with patients being conscious during craniotomy or having stimulating electrodes chronically implanted into parts of the somatosensory pathways, or both. Libet and co-workers were able to recruit some of these patients for a fascinating set of experiments. They showed that, although a single stimulus to the medial lemniscus evoked a normal-looking evoked potential at the cortex, it did not cause a conscious sensation [17]. Stimulation of the lemniscus required a pulse train of up to 500 ms to generate conscious awareness of the stimulus. In addition, they showed that, in contrast with the effect of a single electrical stimulus to the hand which produces a sensation, a single stimulus to the somatosensory cortex does not provoke a sensory experience [16]. It required a train of pulses lasting about 500 ms directly to the cortex before there was any conscious awareness of the stimulus. They concluded from this that, before conscious awareness of a stimulus can occur, it is necessary to achieve a state which they termed *neuronal adequacy*, which takes up to 500 ms to develop

[18]. By comparing differences in the perceived timing of stimuli delivered peripherally and to the medial lemniscus or cortex, they showed that conscious awareness *appears* to occur at about the time of the early cortical evoked response (50 ms). They postulated that, in some way, this serves as a time marker to which the conscious sensation is back-referred.

On reflection, as pointed out by Eccles [19], this back-referral of a conscious experience to an earlier time marker would be essential for the brain to make sense of the outside world if the time for neuronal adequacy varies with modality and with stimulus intensity. It allows the temporal relationships of different inputs to be perceived within an apparently logical time scale, even if the inputs are processed at different rates. An excellent example of how this works in everyday life is the performance of a simple reaction time task. Bearing in mind that neuronal adequacy for awareness takes up to 500 ms, it is remarkable that the minimum reaction time for a simple task may be less than 200 ms! However, the subjective sensation is always that the stimulus is perceived before the task is performed. Whilst this makes sense to the brain, it cannot be the case if conscious awareness occurs 500 ms after the stimulus—that is, as late as 300 ms *after* the response. Both Libet [20] and Cotterill [21] have proposed that conscious awareness is not necessary for the execution of a simple reaction task. However, we propose that what happens, in effect, is that a motor programme is set up by biasing a sequence of synapses so that when the stimulus occurs the reaction task is automatically performed. Consciousness is undoubtedly necessary for this programme to be set up and kept in a state of readiness, but it is a common observation that if the subject's attention wanders, the reaction time becomes very long. However, provided that the subject remains in a state of readiness, the reaction occurs automatically and the outcome then reaches conscious awareness.

How, then, does this relate to the problem of detecting conscious awareness in an apparently anaesthetized patient? The model of consciousness proposed by Libet and colleagues [18] allows us to postulate three ways in which anaesthesia could interfere with conscious awareness. First, it could interfere with the development of neuronal adequacy. Second, it could interfere with the establishment of the time marker of the sensory experience and the subjective referral to it. This would lead to a distorted perception of the outside world. Third, as is common experience, anaesthesia interferes with recall of the conscious experience. This loss of recall implies that reported cases of conscious awareness in anaesthetic practice are only the tip of an iceberg. This might be convenient medico-legally, but it seriously hampers our understanding of the effects of anaesthesia on conscious awareness. The early cortical evoked responses might give us some information about the subjective timing of a conscious sensory experience, in addition to reflecting the global effects of anaesthesia on brain cells. However, to get at conscious awareness itself we need to look at the EEG over the time that neuronal adequacy is developing, that is up to 500 ms after the stimulus. Our group has made a start in this direction by looking at the effects of nitrous oxide on the P300, which is the wave occurring at about 300 ms in the auditory evoked potential [22]. It is clear from these studies that the anaesthetic concentration required to inhibit conscious awareness produces a considerable attenuation of the amplitude of the P300. However, this concentration of nitrous oxide produces a trivial effect on the amplitude and latency of earlier cortical waves (50 ms) which are the back-referral time markers. This is consistent with our observation that a slightly smaller concentration of nitrous oxide permits an accurate reaction time test, but with no registration of the event in memory. Further studies are needed with other anaesthetics to determine if the P300 will be a useful marker of conscious awareness in the apparently anaesthetized patient.

These neurophysiological studies underline the fact that, if we wish to be able, before the end of this century, to detect the awake, paralysed patient with some certainty, then we need to turn our attention away from indirect phenomena that may or may not be related to conscious awareness and attempt to learn about the mechanisms of consciousness from our colleagues in neurophysiology and psychology.

*J. Jessop and J. G. Jones*

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# EFFICIENCY OF AN ENCLOSED AFFERENT RESERVOIR BREATHING SYSTEM DURING CONTROLLED VENTILATION

P. M. DROPPERT, G. MEAKIN, P. C. W. BEATTY, A. J. MORTIMER AND T. E. J. HEALY

## SUMMARY

*We describe an enclosed afferent reservoir (EAR) breathing system developed by Ohmeda and designed to operate efficiently in spontaneous and controlled ventilation. The efficiency of the system was evaluated by calculating the fractional utilization of fresh gas in 10 ASA I–III patients during anaesthesia with controlled ventilation. Maximum efficiency occurred when the minute ventilation to fresh gas flow ratio was greater than 1.5. Under these conditions, fractional utilization was relatively constant with a value of 0.73 (95% confidence interval 0.69–0.78). The minimum fresh gas flow for use during controlled ventilation was determined in another eight ASA I–III patients when the minute volume to fresh gas ratio was greater than 1.5. In view of an increased arterial to end-tidal carbon dioxide partial pressure difference in patients in the first part of the study (1.03 kPa), normocapnia was defined as an end-tidal carbon dioxide partial pressure of 4.3 kPa. Normocapnia was achieved with a mean fresh gas flow of 66 ml kg$^{-1}$ min$^{-1}$, while 70 ml kg$^{-1}$ min$^{-1}$ produced mild hypocapnia.*

***KEY WORDS***

*Equipment: Breathing systems, EAR system*

In recent years, there has been great interest in the development of an "ideal" breathing system capable of being used efficiently during both spontaneous and controlled ventilation. One proposed system is the enclosed afferent reservoir system (EAR) [1–4]. This paper describes a new version of the EAR developed by Ohmeda and the clinical studies to determine its efficiency during controlled ventilation.

## APPARATUS

The EAR (fig. 1) is essentially a modification of the Magill or Mapleson A system [5]. Fresh gas flow enters a rising bellows enclosed in a transparent plastic container on the inspiratory limb of the system. The expiratory limb passes back to a one-way expiratory valve at the base of the container. During spontaneous ventilation, the patient breathes from the enclosed bellows and inspiratory limb, but is prevented from breathing gas contained in the expiratory limb by the closure of the one-way valve. On expiration, gas passes back into the inspiratory tube until the rising bellows is full, at which time the one-way valve opens, allowing gas to be vented from the system; thus the system functions as a Mapleson A with a distal expiratory valve.

Controlled ventilation may be effected by means of a mechanical ventilator or a self-inflating bag. In both instances the expiratory valve is closed tightly during lung inflation by pressure in the bellows container, opening only when the bellows refills at end-expiration. This is an important difference between the EAR and the standard Mapleson A, as the latter allows some fresh gas and deadspace gas to be vented during inflation via a partly opened expiratory valve [6].

In the development of the present prototype, great care was taken to ensure correct functioning

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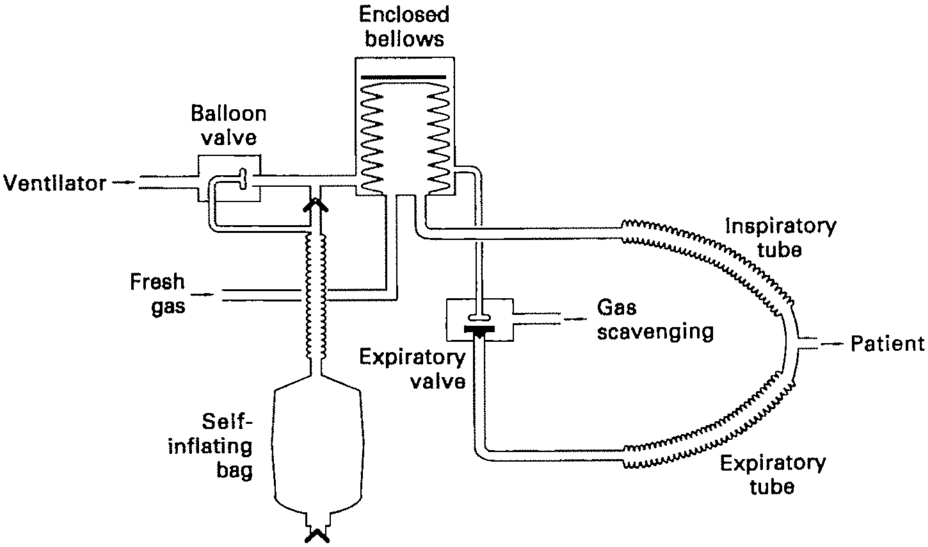

FIG. 1. Diagram of the enclosed afferent reservoir breathing system.

of the expiratory valve. During bench tests, the operation of the valve was observed directly via the gas scavenging aperture (fig. 1). The opening pressure of the valve was set at 1.9 cm $H_2O$—greater than the pressure required to inflate the bellows. The valve was tested also before clinical use by occluding the patient Y-piece and allowing the bellows to fill with oxygen at a flow rate of 200 ml $min^{-1}$. The ability of the bellows to fill completely under these conditions and stay full even after the valve opens, indicates that the valve is operating correctly and that the breathing system is leak-free.

The ventilator used in the present study was the Ohmeda 7800. This is a volume-preset, time-cycled ventilator fitted with internal and external alarm sensors. The internal sensor consists of a pressure transducer while the external sensor, which is situated between the patient and the breathing system, comprises a rotary flow transducer.

## SUBJECTS AND METHODS

The study was approved by the Ethics Committee of South Manchester Health Authority. We studied 18 patients (mean age 69 yr (range 56–85 yr), ASA class I–III) during anaesthesia with controlled ventilation. Anaesthesia was induced with propofol 1–2 mg $kg^{-1}$ followed by vecuronium 0.1 mg $kg^{-1}$ and fentanyl 1–2 μg $kg^{-1}$. The trachea was intubated with a cuffed tracheal tube and anaesthesia was maintained with 66% nitrous oxide and 1–2% isoflurane in oxygen. Ventilation was controlled by means of an Ohmeda 7800 ventilator with an I:E ratio of 1:2.

In the first part of the study, the fractional utilization of fresh gas was determined in 10 patients at various ratios of minute ventilation to fresh gas flow ($\dot{V}_E:\dot{V}_F$). The term fractional utilization denotes the proportion of fresh gas which takes part in gas exchange; it can be derived from the alveolar gas equation as follows:

$$F_{A_{CO_2}} = \frac{\dot{V}_{CO_2}}{\dot{V}_A} \tag{1}$$

where $F_{A_{CO_2}}$ = fractional concentration of alveolar carbon dioxide; $\dot{V}_{CO_2}$ = carbon dioxide production; $\dot{V}_A$ = alveolar ventilation.

In a breathing system, $\dot{V}_A$ is that fraction of the fresh gas flow which takes part in gas exchange. Thus:

$$\dot{V}_A = F_U \cdot \dot{V}_F \tag{2}$$

where $\dot{V}_F$ = fresh gas flow; $F_U$ = fractional utilization of fresh gas.

Substituting in (1) and rearranging we have:

$$F_U = \frac{\dot{V}_{CO_2}}{\dot{V}_F \times F_{A_{CO_2}}} \tag{3}$$

Initial settings of $\dot{V}_E$ and $\dot{V}_F$ were guided by

TABLE I. *Minute volumes* ($\dot{V}_E$) *and fresh gas flow rates* ($\dot{V}_F$) *used in first part of study*

| $\dot{V}_E$ (ml kg$^{-1}$ min$^{-1}$) | $\dot{V}_F$ (ml kg$^{-1}$ min$^{-1}$) | $\dot{V}_E$: $\dot{V}_F$ |
|---|---|---|
| 100 | 40 | 2.5 |
| 100 | 50 | 2.0 |
| 70 | 47 | 1.5 |
| 70 | 70 | 1.0 |
| 70 | 88 | 0.8 |
| 70 | 100 | 0.7 |
| 70 | 117 | 0.6 |
| 70 | 140 | 0.5 |
| 60 | 150 | 0.4 |

laboratory test results. Subsequently, the tidal volume was maintained at 12 ml kg$^{-1}$ and ventilatory frequency and $\dot{V}_F$ were adjusted to produce $\dot{V}_E$: $\dot{V}_F$ ratios of 0.4–2.5 (table I).

At least 20 min was allowed for equilibration at each fresh gas flow. The effluent gas volume and the mixed effluent carbon dioxide concentration were measured over a period of 2–5 min using a mixing box, dry gas meter and a mass spectrometer (Ohmeda MGM 6000). From these measurements, $\dot{V}CO_2$ was calculated. Simultaneously, samples of radial arterial blood were taken for measurement of $Pa_{CO_2}$. *F*U was plotted against $\dot{V}_E$:$\dot{V}_F$ and a best fit curve with 95% confidence limits was generated using a Compaq 286 computer and the Techni-Curve statistical package (Aston Scientific Ltd). The confidence limits indicate the range within which we are 95% confident that the population curve lies [7].

In the second part of the study, the minimum fresh gas flow required to ensure normocapnia during controlled ventilation was determined in eight patients. In order to optimize utilization of fresh gas, $\dot{V}_E$: $\dot{V}_F$ was maintained greater than 1.5. Tidal volume was set at 12 ml min$^{-1}$. Fresh gas flow was reduced progressively from 100 to 20 ml kg$^{-1}$ min$^{-1}$, and end-tidal partial pressure of carbon dioxide ($P\text{E}'_{CO_2}$) was measured using the mass spectrometer after an equilibration period of 20 min at each new flow rate. $P\text{E}'_{CO_2}$ was plotted against $\dot{V}_F$ and a best fit curve with 95% confidence limits was derived using the Techni-Curve regression analysis program.

## RESULTS

The mean weight of patients in the first part of the study was 68 kg and their mean carbon dioxide output was 167.5 ml min$^{-1}$. The mean difference in arterial to end-tidal partial pressures of carbon dioxide ($Pa_{CO_2} - P\text{E}'_{CO_2}$) in these patients was 1.03 kPa.

From figure 2 it may be seen that fractional utilization of fresh gas increased until $\dot{V}_E$: $\dot{V}_F$ reached 1.5. The mean value of 14 measurements performed when $\dot{V}_E$: $\dot{V}_F$ exceeded 1.5 was 0.73 (95% confidence interval 0.69–0.78).

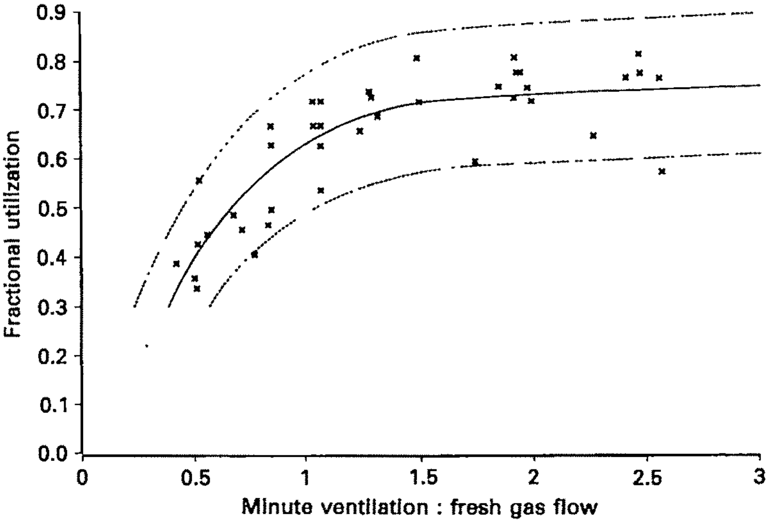

FIG. 2. Fractional utilization of fresh gas plotted against minute volume : fresh gas flow ratio. Data from 10 anaesthetized ASA I–III patients during controlled ventilation. Broken lines represent 95% confidence limits as calculated by the Techni-Curve statistics program.

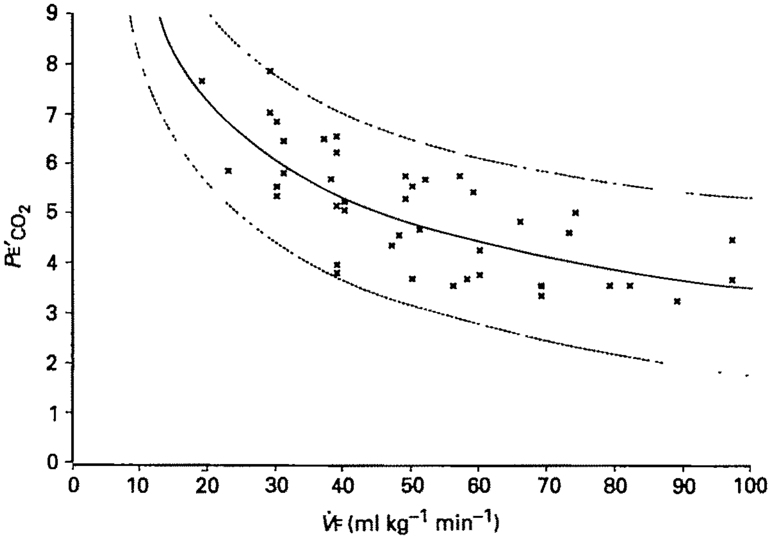

FIG. 3. Variation of end-tidal partial pressure of carbon dioxide ($PE'_{CO_2}$) with fresh gas flow ($\dot{V}F$). Data from eight anaesthetized ASA I–III patients during controlled ventilation when $\dot{V}E:\dot{V}F$ was greater than 1.5. Normocapnia was defined as $PE'_{CO_2}$ 4.3 kPa. Broken lines indicate 95% confidence limits as calculated by the Techni-Curve statistics program.

In the second part of the study, $PE'_{CO_2}$ was related inversely to $\dot{V}F$ (fig. 3); a mean fresh gas flow of 66 ml kg$^{-1}$ min$^{-1}$ resulted in $PE'_{CO_2}$ 4.3 kPa, which should correspond to normocapnia in this group of patients. A fresh gas flow rate of 70 ml kg$^{-1}$ min$^{-1}$ produced mild hypocapnia.

## DISCUSSION

Fractional utilization of fresh gas defines the efficiency of a semi-closed breathing system in terms of the proportion of fresh gas which takes part in gas exchange. Arterial carbon dioxide measurements are necessary for its measurement, as these approximate closely to the mean concentration of carbon dioxide in perfused alveoli [8]. Although the term "fractional utilization" is attributed to Conway [9], the concept was used earlier by Snowdon and colleagues [10] to describe the efficiency of two circle systems without an absorber during controlled ventilation. As a measure of efficiency, it has the advantage over end-tidal or arterial measurements of carbon dioxide in that it is independent of carbon dioxide production. It should, therefore, provide a useful basis for comparing the efficiency of different types of semi-closed breathing systems.

Because fractional utilization depends on the gas exchange properties of the lungs, it is reasonable to ask if the inclusion of some ASA III patients in the present study may have affected our results. ($Pa_{CO_2}-PE'_{CO_2}$) in patients in the first part of the study, 1.03 kPa, is slightly greater than that reported previously in healthy anaesthetized adults (0.7 kPa) [8]. The fraction of unperfused alveoli corresponding to these differences may be calculated using the following formula [11]:

$$\frac{(Pa_{CO_2}-PE'_{CO_2})}{Pa_{CO_2}} \tag{4}$$

From the above, ($Pa_{CO_2}-PE'_{CO_2}$) in our patients corresponds to an alveolar deadspace of 19%, while that of healthy patients corresponds to 13%. These values suggest that the increased ($Pa_{CO_2}-PE'_{CO_2}$) in our patients should not have reduced the efficiency of the breathing system by more than 6%.

Our finding that the maximum utilization of fresh gas with the EAR during controlled ventilation was 70–80% may be surprising in view of the claim by Miller and Miller that it should be easy to achieve 100% utilization of fresh gas with this type of system [4]. However, these authors seem to have assumed that the same efficient shunting of gas fractions found during spontaneous ventilation in Mapleson A type systems occurs in the EAR during controlled ventilation. In view of the greater minute volumes and ventilatory flow rates used during controlled ventilation, this seems unlikely. If arterial carbon dioxide data from their studies of the EAR are used to calculate mean fractional utilization, assuming that the mean carbon dioxide output of their patients was the same as ours (15 % less than basal [11]), values in the range 0.70–0.75 are obtained at $\dot{V}\text{E}:\dot{V}\text{F}$ ratios greater than 1.6. These values are similar to the mean value of 0.73 obtained in the present study.

The fractional utilization curve shown in figure 2 is similar to that obtained by Rose and Froese using a Bain system [12], and that obtained by Snowdon and colleagues using one of two circle systems without an absorber with a tidal volume of 750 ml [10]. This suggests that, although there are well-documented advantages of the EAR during spontaneous ventilation [13, 14], there may be little difference in clinical efficiency between the above systems during controlled ventilation. This agrees with the work of Criswell and colleagues, who found only a small difference in $P\text{E}'_{CO_2}$ values in patients during ventilation with an EAR system and the Bain (0.35 kPa), and concluded that they were of similar clinical efficiency [15].

When interpreting the data from figure 3, it is important to note that these are end-tidal measurements of carbon dioxide. In the first part of this study, mean $Pa_{CO_2}$ differed from the $P\text{E}'_{CO_2}$ by 1 kPa, so that normocapnia (mean $Pa_{CO_2}$ 5.3 kPa) corresponded to a mean $P\text{E}'_{CO_2}$ of 4.3 kPa. From figure 3, the mean $\dot{V}\text{F}$ required to maintain this value of $P\text{E}'_{CO_2}$ was 66 ml kg$^{-1}$ min$^{-1}$, while a $\dot{V}\text{F}$ of 70 ml kg$^{-1}$ min$^{-1}$ produced mild hypocapnia. Allowing for differences in methodology, these results are in agreement with those of Keeri-Szanto [1], Miller and Miller [4] and Chriswell and colleagues [15], but not with those of Bruce and Soni [16] whose prototype EAR required a mean $\dot{V}\text{F}$ of 100 ml kg$^{-1}$ min$^{-1}$ to maintain a mean $P\text{E}'_{CO_2}$ of 5.0 kPa. The latter suggest that the inefficiency of their system was caused by the expiratory valve opening prematurely, allowing fresh gas to displace deadspace gas stored in the inspiratory tube.

In summary, an EAR breathing system has been described which is designed for use during spontaneous and controlled ventilation. During controlled ventilation the system had a maximum efficiency in the use of fresh gas of 70–80 %, which is similar to that obtained with a Bain system and some circle systems without an absorber. In practice, provided $\dot{V}\text{E}:\dot{V}\text{F}$ is greater than 1.5, a fresh gas flow of 70 ml kg$^{-1}$ min$^{-1}$ should be sufficient to maintain mild hypocapnia in adults.

## ACKNOWLEDGEMENTS

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# SPREAD OF INJECTATE AFTER STELLATE GANGLION BLOCK IN MAN: AN ANATOMICAL STUDY

M. GUNTAMUKKALA AND P. A. J. HARDY

## SUMMARY

*Stellate ganglion injections were performed using methylene blue 20 ml in 20 cadavers before postmortem examination. There was spread of solution into the posterior mediastinum and over the apical pleura. There was no spread onto the thoracic sympathetic chain.*

### KEY WORDS

*Anatomy: stellate ganglion. Anaesthetic techniques, regional: stellate ganglion block*

Injection of solutions onto the precervical fascia in man has been used to block the cervicothoracic sympathetic outflow in the so-called "stellate ganglion block". It has been claimed that the injected solution spreads to cover the upper thoracic ganglia [1]. A recent study showed that functional sympathetic block did not occur in thoracic dermatomes [2].

The sympathetic chain lies anterior to the vertebral bodies in the neck, but as it descends across the first thoracic vertebral body, it lies lateral to the vertebral body [3]. From T1 caudally, the sympathetic chain descends in a subpleural plane across the necks of the ribs. In the lower thorax, at the origin of the splanchnic nerves, the sympathetic chain starts to resume an anterior relation to the vertebral bodies, which is maintained into the lumbar region. A study was performed in cadavers using methylene blue 20 ml to observe the pattern of intrathoracic spread after stellate ganglion injection.

## METHODS AND RESULTS

A study was performed in a series of 20 (13 male) cadavers in the mortuary before postmortem. The age at death varied from 22 to 95 yr. A standard anterior stellate ganglion injection was performed in each. A 23-gauge needle was inserted lateral to the trachea at the level of the cricoid cartilage in an antero–posterior direction to contact bone. The needle was withdrawn 0.5 cm and 0.01% methylene blue solution 20 ml injected.

A standard anterior postmortem was performed, with great care during handling of the lung and pleura on the injected side. The lung was retracted in an anteromedial direction and the relation of the injected methylene blue to the anatomical structures noted. If the solution was not visible through the pleura, a note of the position of the solution was made during evisceration.

Solution was observed to lie in the posterior mediastinum in the prevertebral plane (fig. 1) and noted to spread from the neck caudally to T3 ($n =$

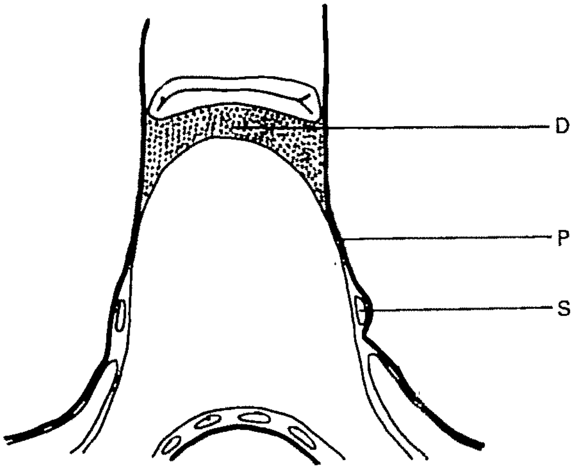

FIG. 1. Diagrammatic cross-section at T2 showing plane of dye spread (D) in relation to the sympathetic chain (S) and pleura (P).

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2), T4 ($n = 17$) or T5 ($n = 1$). In some cases, solution was observed over the apical parietal pleura. In none of the cases did the injected dye spread onto the lateral subpleural surface of the vertebral bodies in the region of the sympathetic chain.

## DISCUSSION

In the present series of observations in cadavers, an attempt was made to provide an anatomical explanation for the physiological failure of stellate ganglion block to produce thoracic ganglion block [2]. It is possible that the spread of dye in cadavers differs from the spread of local anaesthetic *in vivo*. In some cases (for example intercostal blocks) which lie within the surgical field, it may be possible to observe spread *in vivo* under direct vision, but even then spread of dye solution may differ from spread of local anaesthetic. This type of study is not possible with stellate ganglion block. The use of aqueous methylene blue was better than previous injection techniques which used more viscous solutions [1] which may have created artefact.

From our observations, it would appear that in cases where block of the thoracic portion of the sympathetic chain is desired, this will not be achieved by stellate ganglion block. The only way to ensure thoracic sympathetic block is to block the chain directly [4] or indirectly, for example during interpleural block [5].

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# ADRENALINE, FENTANYL OR ADRENALINE AND FENTANYL AS ADJUNCTS TO BUPIVACAINE FOR EXTRADURAL ANAESTHESIA IN ELECTIVE CAESAREAN SECTION

D. W. NOBLE, L. M. MORRISON, M. S. BROCKWAY
AND J. H. McCLURE

## SUMMARY

*We have compared the effects of extradural fentanyl and fentanyl plus adrenaline with adrenaline alone as adjuncts to extradural bupivacaine in patients undergoing elective Caesarean section. Forty-five patients were allocated randomly to receive 0.45% bupivacaine 20 ml with adrenaline 4.5 µg ml$^{-1}$, fentanyl 4.5 µg ml$^{-1}$ or adrenaline plus fentanyl (4.5 µg ml$^{-1}$ of each) as supplements. The main outcome measures were time to bilateral analgesia of T6 or higher, need for intraoperative analgesic supplements, observer rating of intraoperative analgesia and patient assessment of analgesia using a 10-cm visual analogue scale. The time to onset of analgesia to T6 was reduced insignificantly by the fentanyl solutions compared with adrenaline only. The quality of analgesia as assessed by the need for analgesic supplements was superior for the patients given fentanyl. An observer rating of pain and visual analogue pain scoring by the patient also indicated superior analgesia with fentanyl supplementation. Two patients experienced respiratory depression after extradural fentanyl and were given naloxone. Two neonates were also given naloxone. Close supervision is therefore recommended in the early postoperative period when this technique is used.*

***KEY WORDS***

*Anaesthetic techniques extradural Anaesthetics, local· bupivacaine Analgesics. fentanyl.*

The advantages of extradural anaesthesia for Caesarean section are well documented [1–3]. However, disadvantages include slow onset time, which may preclude its use for urgent procedures, and visceral pain, which is experienced by approximately 50% of patients [4]. Adrenaline has been shown to improve the efficacy of extradural block [5] and until recently has been the only adjunct available for this purpose. More recently, the role of extradural opioids has been investigated in enhancing the analgesic effect of local anaesthetics. Because of its rapid onset of action and lipid solubility, which theoretically reduces rostral spread in cerebrospinal fluid, fentanyl is considered to be a suitable opioid for extradural administration [6]. Peak plasma concentrations of fentanyl are smaller after extradural administration compared with the i.m. route [6] and bolus doses of 50–200 µg administered extradurally have been reported to cause little and only clinically insignificant respiratory depression [6–8]. The addition of fentanyl to local anaesthetic solutions administered extradurally has been shown to improve analgesia for parturients in labour and during Caesarean section [9–13]. In one open study, not only was patient comfort improved, but a significant reduction in onset time was observed when fentanyl 100 µg was added to 0.5% bupivacaine [14]. The object of this randomized, double-blind controlled clinical trial was to ascertain if a useful reduction in onset time may be obtained with fentanyl or fentanyl and adrenaline compared with adrenaline sup-

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plementation only, and to compare the analgesic effectiveness of these three combinations.

## PATIENTS AND METHODS

Following Ethics Committee approval, we studied 48 healthy mothers undergoing elective Caesarean section under extradural anaesthesia, after obtaining their informed consent.

Patients who were less than 152 cm in height, or more than 100 kg in weight were excluded in order to reduce the risks of excessive spread from a standardized single dose of local anaesthetic. Those with pregnancy-induced hypertension were excluded also because of the potential adverse effects of adrenaline on maternal haemodynamics and uterine blood flow. Based on the results of an open study [14], taking a clinically significant reduction in onset time to be 10 min, and a statistically significant difference to be $P < 0.05$, it was calculated that 15 patients per group would achieve a power of greater than 0.80.

Patients were premedicated orally on the evening before, and 2 h before the procedure, with ranitidine 150 mg and were given also sodium citrate 30 ml on arrival in the anaesthetic room. An i.v. infusion of Hartmann's solution 10 ml $kg^{-1}$ was commenced. Patient monitoring included ECG, non-invasive arterial pressure measurement (Dinamap) and pulse oximetry.

Patients were allocated randomly to receive 20 ml of 0.45% bupivacaine with adrenaline 4.5 $\mu g\ ml^{-1}$ (group I), 0.45% bupivacaine with fentanyl 4.5 $\mu g\ ml^{-1}$ (group II) or 0.45% bupivacaine with adrenaline 4.5 $\mu g\ ml^{-1}$ plus fentanyl 4.5 $\mu g\ ml^{-1}$ (group III), in a double-blind design, via a lateral-eyed extradural catheter inserted 4 cm into the extradural space between the second and third lumbar vertebrae.

The solutions were constituted by adding fentanyl 100 µg or 0.1 ml of adrenaline 1 mg $ml^{-1}$, or both, to 0.5% bupivacaine 20 ml; saline was used as required to give a total volume of 22 ml of solution.

After insertion of the catheter, and with the patient in the left lateral position, 5 ml of the solution was injected as a test dose 5 min before injection of the main dose. The main dose was injected in three 5-ml aliquots, each aliquot being administered over 15 s followed by a pause of 45 s between aliquots. Onset of block was timed from the end of the last injection.

Before delivery of the infant, oxygen was administered via a 60% Ventimask; thereafter, it was discontinued. Hypotension, defined as a systolic arterial pressure of less than 90 mm Hg or a reduction of more than 30% from baseline, was treated with ephedrine and fluids. Nausea and vomiting were treated with ephedrine (if hypotension-related) or metoclopramide.

Sensory block was assessed by a blinded observer using loss of sensation of pinprick by the blunt end of a 27-gauge dental cartridge needle. Motor power was assessed using the Bromage scale. These assessments were made at 2, 5, 10, 15, 20, 25 and 30 min. The times for sensory block to develop bilaterally to T10 and T6 were noted, with the maximum height of block and time to maximum block.

If a bilateral sensory block of T6 or higher was not present at 30 min, further 5-ml aliquots of bupivacaine were administered until an adequate height of block was achieved. Increments of local anaesthetic, or i.v. diamorphine, were administered to treat moderate pain or persistent discomfort as indicated clinically. In general, anatomically localized pain was treated with additional local anaesthetic and poorly localized pain or failure of additional local anaesthetic was an indication for i.v. diamorphine after delivery.

The times from skin incision to uterine incision and uterine incision to delivery were noted. The Apgar scores at 1 and 5 min were recorded also.

At the end of the procedure, the blinded observer rated the quality of anaesthesia according to the following scale: excellent; good = minor or transient discomfort; fair = moderate or persistent pain or discomfort requiring supplementation with an i.v. opioid; poor = severe pain requiring induction of general anaesthesia.

At this time the patient was asked also to indicate on a 10-cm visual analogue scale, with "no pain" and "worst pain imaginable" at either end, how much pain they experienced during the procedure. The patient was questioned about other adverse effects (nausea, vomiting, lightheadedness, itching, shivering or any other symptoms she wished to report) shortly after returning to the recovery room and the following day.

Differences between groups were analysed using analysis of variance or the Kruskal–Wallis test followed by Student's *t* test or Mann–Whitney test as appropriate for interval or ordinal data. Differences in proportions were analysed with chi-square or Fisher's exact test.

TABLE I. *Patient characteristics (mean (range or* SD*)).* *P < 0.05 *group I* vs *group II*

| | Group I ($n$ = 15) | Group II ($n$ = 15) | Group III ($n$ = 15) |
|---|---|---|---|
| Supplement | Adrenaline | Fentanyl | Fentanyl + adrenaline |
| Age (yr) | 28.5 (18–36) | 28.9 (18–35) | 29.1 (22–36) |
| Weight (kg) | 74.9 (12.4) | 73.1 (11.3) | 72.4 (7.5) |
| Height (cm) | 165 (6.1) | 161 (4.3)* | 162 (4.1) |
| Pre-op. SAP (mm Hg) | 123 (10.4) | 121 (10.6) | 124 (13.4) |

TABLE II. *Onset of analgesia (mean (*SD*) or median (quartiles)) and motor block (Bromage scale).* †*Patients requiring supplementary local analgesia to reach T6 or higher* *P = 0.02 *group I* vs *group III*

| | Group I | Group II | Group III |
|---|---|---|---|
| Additional analgesia† | 3 | 1 | 1 |
| Time (min) to reach | | | |
| T10 | 10.6 (6.0) | 7.8 (3.9) | 6.2 (3.4)* |
| T6 | 17.7 (7.5) | 16.3 (6.7) | 14.3 (7.0) |
| No. of analgesic dermatomes above L1 | 10.0 (8.0–11.0) | 10.0 (7.0–13.0) | 10.0 (9.0–11.0) |
| Time to maximum spread (min) | 23.3 (4.5) | 22.7 (4.6) | 24.0 (4.7) |
| Motor block | | | |
| 0 | 1 | 3 | 0 |
| 1 | 5 | 7 | 4 |
| 2 | 8 | 4 | 11 |
| 3 | 1 | 1 | 0 |

## RESULTS

Three patients were excluded after randomization: one procedure was interrupted to allow an emergency Caesarean section to proceed; one procedure was abandoned because of unilateral analgesia with no analgesia above L1 on one side; and another procedure was abandoned after a bloody tap was followed by evidence of i.v. injection on reinsertion at another level. All three patients had been allocated to group II.

Patient characteristics were similar, with the exception that patients in group I were taller than those in the other groups (table I).

Three patients in group I required additional local anaesthetic to produce an adequate spread of analgesia, compared with one patient each in the other two groups (table II). Sensory block to T10 was most rapid in group III and the difference was statistically significant from group I. A similar pattern was observed when assessing time to sensory block to T6, but was less marked and was not statistically significant. It is noteworthy that, if the time for the test dose is included seven, six and four patients from groups I, II and III took 25 min or longer to achieve an analgesic block to T6 or higher. The maximum number of analgesic dermatomes above L1 and the times to reach maximum spread were similar in all three groups and maximum motor block was not significantly different between groups (table II).

Three patients in group I and three in group II required further increments of local anaesthetic during the procedure, compared with only one in group III. In addition, nine patients in group I required i.v. diamorphine, compared with two in group II and none in group III (table III). I.v. diamorphine was given after delivery for poorly localized pain or failure of additional local anaesthetic to control pain.

The quality of analgesia as rated by the observer was superior in the fentanyl groups compared with the adrenaline only group, with 13 patients in group III being rated as having "excellent" analgesia and the remaining two patients as having "good" analgesia. In contrast, eight patients in group I were rated as having only "fair" analgesia (table III). The visual analogue scale completed by the parturients reflected this pattern, the lower scores being observed in the fentanyl groups.

TABLE III. *Number of patients requiring supplementary analgesia and quality of analgesia for Caesarean section. Significant differences compared with group I: *P < 0.05; **P = 0.01; ***P = 0.005*

| | Group I | Group II | Group III |
|---|---|---|---|
| Supplementation | | | |
| Local anaesthetic | 3 | 3 | 1 |
| I.v. opioid | 9 | 2* | 0** |
| Quality of analgesia | | | |
| Excellent | 5 | 11* | 13*** |
| Good | 2 | 2 | 2 |
| Fair | 8 | 2 | 0 |
| Poor | 0 | 0 | 0 |
| VAS score ⩾ 2 cm | 6 | 2 | 0 |

TABLE IV. *Number of patients with complications during operation*

| | Group I | Group II | Group III |
|---|---|---|---|
| One or more episodes of hypotension | 8 | 9 | 13 |
| Ephedrine given | 9 | 10 | 13 |
| Nausea | 5 | 5 | 5 |
| Vomiting | 2 | 2 | 0 |
| Metoclopramide given | 7 | 2 | 0 |
| Respiratory depression | 0 | 2 | 0 |
| Naloxone given | 0 | 2 | 0 |

These differences did not reach statistical significance (group I *vs.* group III, $P = 0.051$; group I *vs* group II, $P = 0.13$).

Hypotension was most frequent in group III compared with the other groups and the incidence of nausea or vomiting was similar between groups (table IV).

Two patients in group II were given naloxone for respiratory depression. The first patient has been reported in detail elsewhere [15]. The second patient, who was drowsy from about 10 min after extradural injection, demonstrated decreases in $Sp_{O_2}$ from 96% to less than 90% after delivery. Rousing the patient resulted in larger breaths with quick return of $Sp_{O_2}$ to previous values. Naloxone 0.4 mg i.v. antagonized the patient's somnolence and respiratory depression effectively and there was no recurrence in the recovery room.

Maternal interview in the recovery period and the following day failed to demonstrate significant differences in the incidence of nausea, vomiting, lightheadedness, itching or shivering. Shivering, however, was most frequent in those receiving adrenaline supplementation (47%) and least frequent in those receiving fentanyl (7%)—a finding which is in accordance with others [16].

The Apgar scores at 1 and 5 min were generally satisfactory, with no significant differences between groups. Two neonates, both of whom had Apgar scores of nine at 1 and 5 min received naloxone. One (group II) was "very sleepy" 3 min after delivery (Apgar score of 6) and was given naloxone 20 µg i.m. The other (group III) was observed to have a "persistent blue tinge" at 10 min and received naloxone 60 µg i.m. However, this neonate had aspirated a large volume of liquor and there was no discernible improvement following naloxone.

## DISCUSSION

The results of this study indicate that supplementation of bupivacaine with fentanyl or fentanyl and adrenaline was not associated with clinically useful reduction in onset time of analgesia to T6. These results conflict with those of an earlier open study which found a mean reduction in onset time of more than 10 min [14]. In this study, the mean reduction in analgesic onset was of the order of 3–4 min only. Other studies also have failed to show a reduction in onset time [11–13]. However, these have utilized a slow, multiple increment technique with lengthy periods between increments which might obscure any differences. Spinal anaesthesia to this level or higher can be achieved in about 5 min [17]. In comparison, if the time for the test dose is added to the times reported here, only two of 45 patients studied here could be considered ready for Caesarean section at 10 min and in 17 patients at least 25 min elapsed before bilateral analgesia to T6. The number of analgesic dermatomes was similar in all three groups, despite a tendency for the adrenaline-supplemented group to be taller compared with the other groups. However, statistically significant differences in patient characteristics may occur in correctly conducted randomized trials [18].

The combination of fentanyl and adrenaline appeared to provide the best analgesia with the least requirements for analgesic supplements, the best observer rating and the best visual analogue scores. The fentanyl only group ranked second for these assessments. Although the fentanyl plus adrenaline group ranked first for all analgesia assessments, there were no significant differences between it and the fentanyl only group. The finding of improved analgesia with fentanyl supplementation accords with those of other workers [11–14]. Single doses of 50–200 μg and cumulative doses in excess of this have been reported to cause little or only clinically insignificant respiratory depression [6–8, 19]. Some consider parturients to be at very low risk of respiratory depression because of pregnancy-associated hyperventilation [20], and the dose of fentanyl chosen for this study (100 μg) was anticipated to be both safe and efficacious. The analgesia achieved with extradural fentanyl is superior to that after i.v. or i.m. administration and, perhaps because of sequestration of this lipophilic drug in adipose and neural tissue, the blood or plasma concentrations of fentanyl are smaller after extradural administration [6, 10, 21, 22]. Comparison of supplementary extradural with i.m. fentanyl given before local anaesthetic block for Caesarean section may be more valid scientifically. However, the known pharmacokinetic profile [6, 21], the time of peak plasma concentrations and subsequent placental transfer after i.m. fentanyl may render such a comparison unethical because of the risk of neonatal depression.

Unsupplemented extradural bupivacaine for Caesarean section is associated with an incidence of visceral pain approaching 50% [4] and so there is scope for improvement in maternal comfort. The addition of adrenaline to bupivacaine has been shown to improve its efficacy [5]. However, this study has demonstrated fentanyl to be more efficacious than adrenaline as a supplement to bupivacaine. There was a high incidence of maternal hypotension in this study which may reflect the modest i.v. infusion given to these patients, and the relatively rapid extension of block. This was treated promptly and effectively with ephedrine and additional fluids. However, the most worrying adverse effect seen in this small study was respiratory depression, which occurred in two patients. Although other previously published studies have not documented clinically severe respiratory depression, these studies have been small and the absence of side effects gives only limited reassurance [23]. For example, in one of the larger trials [13], 30 women were allocated randomly to receive extradural fentanyl and bupivacaine. The 95% confidence intervals for any side effect in a trial of this size in which the side effect did not occur is 0–10%.

Extradural fentanyl has been shown to produce increases in $Pa_{CO_2}$ and flattening of the ventilation–$Pa_{CO_2}$ relationship; these effects are greater and of longer duration than those produced by i.m. fentanyl [8], but are probably not of clinical importance [7]. Respiratory arrhythmias have been documented also in a study in which fentanyl 100 μg was used as a supplement to bupivacaine for percutaneous nephrolithotripsy [24]. Interestingly, in that study, the addition of adrenaline to this mixture reduced the incidence of respiratory arrhythmias.

In this study, the relatively rapid injection of solution may have produced a "longitudinal sleeve" of dilute fentanyl within the extradural space, which may have enhanced rostral spread of fentanyl. This effect may not be seen when a similar dose of fentanyl is administered slowly or in a smaller volume. Rostral spread may be the main mechanism of depression, as blood concentrations of fentanyl are small after extradural administration [22]. It has been demonstrated also that dilute solutions of fentanyl have a more rapid onset and more prolonged duration of action [25]. However, as a result of this study, we now believe that close observation is warranted for at least 3 h after administration of similar doses of extradural fentanyl. Further work to examine the efficacy and safety of extradural fentanyl given in smaller doses, or similar dose in a smaller volume is now required.

Two neonates were given naloxone, although both had Apgar scores of 9 at 1 and 5 min. The neonatologists, knowing that the mothers had received an opioid, may have applied a lower threshold for administration of an antagonist, and it is uncertain if these two neonates suffered as a result of administration of opioid. Neonatal neurobehavioural effects were not observed with extradural fentanyl 1 μg kg$^{-1}$ [26, 27] although they have been observed with high doses of extradural sufentanil (80 μg) [28]. However, high umbilical arterial concentrations are encountered occasionally after extradural fentanyl 100 μg and some neonates may be at risk of opioid effects [13].

In conclusion, this study has failed to demonstrate a clinically significant reduction in time to an acceptable level of analgesia for Caesarean section. However, fentanyl supplementation was associated with greater maternal comfort and a reduced requirement for analgesics during operation. Two cases of maternal respiratory depression highlight the need for close observation into the recovery period to avert possible adverse outcome. Neonatologists should be forewarned when extradural opioids are given to the mother before delivery.

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# ZONES OF DIFFERENTIAL SENSORY BLOCK DURING EXTRADURAL ANAESTHESIA

S. J. BRULL AND N. M. GREENE

**SUMMARY**

*We have measured spinal segmental levels of anaesthesia to light touch (LT), pinprick (PP) and cold temperature discrimination (TE) during 2% lignocaine extradural anaesthesia in 22 patients, to determine if zones of differential sensory block develop during extradural anaesthesia and, if so, the extent to which TE extends beyond PP or LT levels and how age affects differential block. The median thoracic dermatomal levels were 4.5 for LT, 2.0 for PP and 2.0 for TE. Zones of differential sensory block developed within 5 min of extradural injection of local anaesthetic, and persisted for the next 55 min. In all instances, PP extended more cephalad than LT, and TE extended above PP levels. There were no differences in the extent of zones between the two groups of patients with mean ages of 28 and 48 yr. Thus, during extradural anaesthesia, sympathetic denervation extended one to two spinal segments above the sensory levels of LT and PP anaesthesia, age (28 vs 48 yr) affected neither the cephalad extent nor the width of zones of differential block, and PP levels of anaesthesia were closer to presumed levels of sympathetic block than were LT levels.*

**KEY WORDS**

*Anaesthetics, local: lignocaine Anaesthetic techniques: extradural.*

Extradural anaesthesia results in denervation of somatic motor, sensory and sympathetic fibres. Patient comfort during surgery depends on the extent of sensory denervation, while cardiovascular and especially arterial pressure responses to anaesthesia depend to a major degree on the extent of sympathetic denervation. However, the zone of differential block between the level of sensory anaesthesia and the level of sympathetic block is unclear. The only published prospective study of the extradural zones of differential block [1] found that the mean levels of sensory anaesthesia were not significantly different from the mean levels at which temperature discrimination was lost. However, it is not clear in this report if "touching the skin with a needle point" measured the level at which light touch was blocked, or if pinprick anaesthesia was measured. More importantly, data on segmental levels of anaesthesia were reported and were analysed statistically as means, not as medians; the latter is preferable, for reasons stated below.

Data on the existence and extent of zones of differential block during spinal anaesthesia are of little value in estimating the extent of these zones during extradural anaesthesia. The width of the zone of differential somatic motor and somatic sensory block averages 2.8 dermatomes [2], significantly less than the average of 4.6 dermatomes which develops during extradural anaesthesia. This provides good evidence that the average dermatomal width of the zone between sensory and sympathetic levels of block during extradural anaesthesia is different from the average of 2 spinal segments [3] present during spinal anaesthesia.

The present study was designed to assess the width of zones of differential block, if any, between light touch, pinprick and temperature (cold) discrimination during extradural anaesthesia under clinical conditions. Further, if zones of differential block were found to exist, the study was designed to determine which level of sensory anaesthesia, light touch or pinprick, might be more indicative of the level of sympathetic denervation. Although it is not a direct function

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of the sympathetic nervous system, temperature discrimination block was used as a clinical correlate of the level of sympathetic denervation [3, 4], as it is the easiest and probably the most reliable method, albeit imperfect, of assessing the extent of sympathetic denervation clinically.

## PATIENTS AND METHODS

After approval by the institutional Human Investigations Committee, verbal informed consent was obtained from 22 patients (age range 22–76 yr), undergoing extradural anaesthesia for elective surgical procedures. All patients (ASA physical status I, II or III) were devoid of known neuromuscular disease and had no contraindications to extradural anaesthesia. Premedication was not prescribed. During operation, midazolam was given in doses sufficient to relieve anxiety without producing undue sedation (0.01–0.05 mg $kg^{-1}$). The dose of fentanyl, the only intraoperative opioid used, was limited to 2 $\mu g\ kg^{-1}$ in the first 45 min after extradural injection of local anaesthetic. In all patients, 2% lignocaine with adrenaline (1:200000) with sodium bicarbonate 0.1 mmol $litre^{-1}$ per ml of solution, was injected extradurally.

During operation, patients were monitored according to our departmental standards for patients undergoing extradural anaesthesia. Dose and speed of injection of local anaesthetic were determined by the resident and attending anaesthetist, who were not involved in the study. In all patients, the extradural space was identified by the loss of resistance technique, using an 18-gauge Weiss needle inserted at the 3rd or 4th lumbar interspace with the patients in the flexed lateral decubitus position. After insertion of an extradural catheter 2–3 cm, tests were made for subarachnoid and intravascular insertion and patients were turned immediately to the supine horizontal position. Local anaesthetic was injected extradurally via the indwelling catheter. The volume and frequency of administration of local anaesthetic were at the sole discretion of the primary anaesthetist, and no attempt was made to standardize the anaesthetic care.

All sensory assessments were performed on the same side of the patient by the same observer (S.J.B.), who did not participate in the perioperative administration of i.v. fluids or medications. The dermatomal levels of anaesthesia to light touch, pinprick and temperature (cold) discrimination were tested and recorded when each modality tested had progressed to at least the T12 dermatome [5]. These levels, and mean arterial pressure and heart rate were measured every 5 min for 30 min, and thereafter every 15 min, until 60 min from the initial injection of local anaesthetic. In addition, total cumulative volumes of i.v. crystalloid solutions administered, doses of vasoactive i.v. agents, if any, and total cumulative dose of local anaesthetic injected extradurally were recorded at the same times. I.v. crystalloid solutions, i.v. vasoactive medications and extradural local anaesthetics were administered according to clinical criteria, and were not influenced by study design.

The most cephalad dermatomal level of loss of each sensory modality was determined by asking the patient to compare differences between sensory stimuli applied to an unanaesthetized area (e.g., the shoulder tip) and to the trunk in the midclavicular line. The level caudal to the lowest level at which light touch was first discerned was considered the most cephalic level of light touch block. The level caudal to the lowest dermatome at which the sensory stimulus felt the same as at the shoulder tip was considered the most cephalic level of block of the sensory modality (pinprick or temperature) being tested. Light touch was measured by applying the dull, hinged end of a sterile safety pin to the skin without indenting it. Pinprick was measured using the sharp tip of a sterile safety pin protruding 3 mm beyond a rubber stopper. Temperature was measured by spraying the skin with a non-toxic, non-flammable, highly volatile mixture of dichlorofluoromethane and trichloromonofluoromethane (FluoriMethane, Gebauer, Cleveland, Ohio) [6]. Arterial pressure was measured using an automated sphygmomanometer, and heart rate was measured from the ECG. The 22 patients were classified into two groups, according to the median age: less than (or equal to) 35 yr, and older than 35 yr.

Although sensory levels of spinal and extradural anaesthesia are almost invariably reported as averages, or means, they represent ordinal, not interval data, as do group Apgar scores and ASA physical status ratings, and are presented, therefore, as medians, with ranges, rather than means and SD or SEM [7, 8]. The widths of zones of differential block, being interval data, are presented in this study as means (SD). Spinal segmental levels of denervation, being ordinal

TABLE I. *Details of the 22 patients grouped according to median age. LA = total volume of local anaesthetic (lignocaine) injected extradurally by the indicated observation time*

| | Median age ⩽ 35 yr | Median age > 35 yr |
|---|---|---|
| *n* | 12 | 10 |
| Mean (SD) age (yr) | 28 (5) | 48 (11) |
| Weight (kg) | 78.8 | 70.8 |
| Height (cm) | 164.9 | 165.6 |
| LA at 5 min (ml) | 7.5 (3.2) | 7.5 (3.1) |
| LA at 15 min (ml) | 18.4 (2.7) | 19.3 (3.5) |
| LA at 60 min (ml) | 31.3 (3.5) | 27.0 (1.4) |

TABLE II. *Mean, median and 25th–75th percentiles light touch (LT), pinprick (PP) and cold temperature (TE) discrimination. All dermatomes are thoracic except for C7.0, which denotes the 7th cervical dermatome*

| | Sensory modality | | |
|---|---|---|---|
| Dermatomal extent | LT | PP | TE |
| Mean | 4.5 (2.6) | 2.6 (2.1) | 1.5 (2.5) |
| Median | 4.5 | 2.0 | 2.0 |
| 25th–75th percentile | 2.5–6.5 | 1.0–4.0 | C7.0–4.0 |

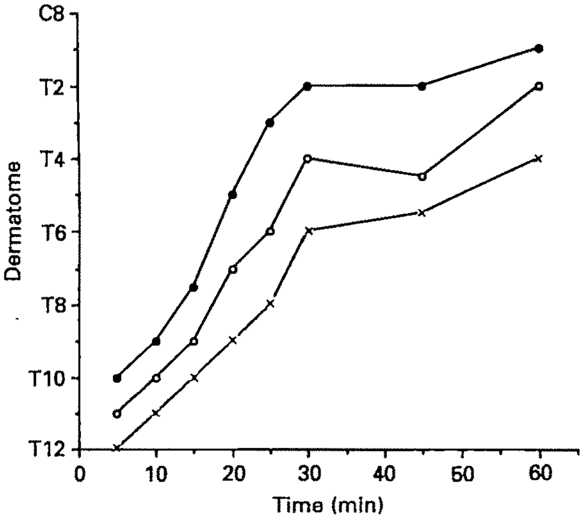

FIG. 1. Thoracic (T) or cervical (C) dermatomal levels of light touch (x), pinprick (○) and cold temperature (●) denervation as a function of time during extradural anaesthesia.

TABLE III. *Mean (SD) width (dermatomes) of light touch to pinprick (LT–PP) and pinprick to temperature (PP–TE) zones of differential anaesthesia as a function of time.* n = *Number of observations at each time interval*

| | LT–PP | | PP–TE | |
|---|---|---|---|---|
| Time | *n* | Width | *n* | Width |
| 5 min | 8 | 1.0 (0.5) | 12 | 1.3 (0.6) |
| 10 min | 13 | 1.8 (2.0) | 22 | 1.1 (0.9) |
| 15 min | 18 | 1.5 (0.7) | 22 | 1.1 (1.2) |
| 20 min | 20 | 1.8 (0.9) | 22 | 1.4 (0.8) |
| 25 min | 19 | 2.3 (1.3) | 21 | 1.6 (1.4) |
| 30 min | 21 | 2.3 (1.6) | 21 | 1.6 (1.3) |
| 45 min | 10 | 2.6 (1.6) | 10 | 1.3 (1.0) |
| 60 min | 5 | 2.8 (3.1) | 5 | 1.2 (1.6) |

data, are presented as median (and 25th–75th percentiles). However, because most readers are accustomed to mean (SD) data for group levels of extradural anaesthesia, these are included also. Ordinal (non-parametric) data were analysed using Wilcoxon rank sum test or, where appropriate, by Wilcoxon signed rank test for paired data. Interval (parametric) data were analysed by *t* test for independent samples or, where appropriate, paired *t* test. Statistical significance was defined as $P < 0.05$ for all analyses.

## RESULTS

The four males and 18 females in the study had a mean age of 38.6 yr (range 22–76 yr), mean weight 75.2 (15) kg, and mean height 165.3 (9) cm. Five of the patients were ASA physical status I, 14 were ASA II, and three were ASA III. Details of the 22 patients grouped according to their median age of 35 yr are represented in table I.

The highest, most cephalic dermatomal level for light touch was T4.5 (SD 2.6), for pinprick T2.6 (2.1) and for temperature T1.5 (2.5) ($P < 0.05$ for the differences between each of the three sensory modalities). The most cephalic median dermatomal levels (with 25th–75th percentiles) for light touch, pinprick and temperature are shown in table II. Changes in the dermatomal extent for each of the three sensory modalities are shown in figure 1. Analysis of the denervation level of three sensory modalities revealed no significant differences in the most cephalic extent in the group of patients younger than 35 yr compared with the older group.

The difference between the levels of light touch (LT) and pinprick (PP) (i.e., the zone of differential block between light touch and pinprick sensory modalities), and the zone of differential block between pinprick and tempera-

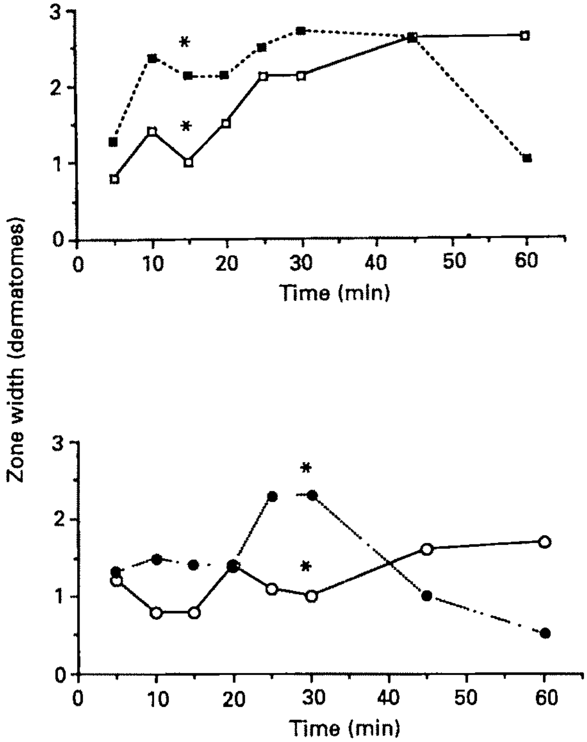

FIG. 2. Width (number of dermatomes) of zones of differential block as a function of age. □ = LT–PP, age ⩽ 35 yr; ■ = LT–PP, age > 35 yr; ○ = PP–TE, age ⩽ 35 yr. ● = PP–TE, age > 35 yr. *$P < 0.05$.

ture (TE), was statistically significant at 5 min (i.e., the LT–PP and PP–TE zones of differential block were both statistically different from zero at the 5-min observation time). These zones of differential anaesthesia remained constant and statistically different from zero over the entire study ($P < 0.05$) (table III). The width of the LT–PP zone (mean 1.0 (0)) in patients younger than 35 yr was statistically less than in the older group (mean 2.1 (0.6)) at the 15-min interval. Similarly, the width of the PP–TE zone (1.0 (0.7)) in the patients younger than 35 yr was statistically less than that in the older group (mean 2.3 (1.5)) at 30 min (fig. 2).

The mean width of the LT–PP zone was 1.0 (0.5) dermatomes. The tendency of this zone to increase its width over time did not reach statistical significance. Similarly, the width of the PP–TE zone of differential sensory block remained statistically unchanged during the study (table III), even as the levels of sensory denervation continued to increase (fig. 1).

The mean total volume of local anaesthetic administered over the 60-min observation period was 29.6 ml, 7.5 ml of which was administered in the first 5 min, inclusive of 5.0 ml used for test doses for subarachnoid (2 ml) and intravascular (3 ml) injection (table I). There were no significant differences in the group of patients older than 35 yr compared with the younger group with respect to total dose of local anaesthetic, dose of local anaesthetic at each measurement time, dose of i.v. fentanyl or vasoactive substances, total amount of i.v. fluids, or haemodynamic state as reflected by changes in mean arterial pressure or heart rate.

## DISCUSSION

This study has shown that extradural anaesthesia, in common with spinal anaesthesia, is associated with zones of differential sensory block, and contradicts the results of a previous study [1].

The time at which these zones of differential anaesthesia reached statistical significance was 5 min or less. When these zones had appeared, they remained unchanged over the entire study. Although there was a tendency for the LT–PP zone width to increase with time, this did not reach statistical significance during the 60 min of observation. The width of the PP–TE zone also remained constant over time. Although the total dose of extradural local anaesthetic required to achieve a given anaesthetic level is greater than the dose required to achieve the same level of sensory denervation with spinal anaesthesia, it appears that both regional techniques are associated with development and maintenance of zones of differential sensory block [6].

The mechanisms of these zones of differential block are unknown during both extradural and spinal anaesthesia. However, the existence of these zones is important, as it demonstrates that for any given pinprick sensory level, the extent of sympathetic denervation (assessed by level of temperature anaesthesia) is always more extensive than either pinprick or light touch sensory levels. Although the widths of LT–PP at 15 min and PP–TE at 30 min were both less in the group of patients younger than 35 yr, this difference was not apparent at any other time. Therefore, in the relatively narrow age range studied in the present report, age did not appear to influence either cephalic extent or the width of zones of differential block. These findings are consistent with other reports which have shown that the relationship between age and extradural dose requirements is linear in patients aged 20–40 yr; however, this relationship is not maintained in patients older than 50 yr [9]. It is possible that the width of the zones of differential block might also be different in patients older than 50 yr.

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# COMPARISON OF SPEED OF ONSET OF ANALGESIC EFFECT OF DIAMORPHINE AND MORPHINE

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## SUMMARY

*In a random, double-blind crossover trial using an ischaemic limb pain model we have assessed the speed of onset of analgesia after an i.v. bolus of equipotent doses of diamorphine and morphine in 12 healthy male volunteers. Pain and its subsequent relief were assessed by means of a visual analogue scale. Two of the subjects found diamorphine acted quicker than morphine, one found no difference and nine found that morphine was quicker than diamorphine. The mean time to diamorphine effect was 53% greater than for morphine ($P < 0.005$, Wilcoxon rank sum test). These findings suggest that, for rapid relief of pain, morphine is more suitable than diamorphine.*

*KEY WORDS*

*Pharmacology · morphine, diamorphine*

Morphine and diamorphine are used frequently for analgesia in the U.K. After operation, these drugs are often given i.v. for pain relief in small increments until effective analgesia is achieved [1, 2]. The speed of onset of action of the drug is important in determining the analgesic dose because further doses should not be administered until the full effect of a previous dose is obtained. The response to an i.v. bolus of diamorphine is often stated to be quicker than for morphine. This is attributed to its greater lipid solubility which may allow easier passage of diamorphine across the blood–brain barrier [3–5].

We could find no data to support this contention and therefore have compared the onset of action of morphine and diamorphine after i.v. injection using an ischaemic limb pain model which has been described by other workers [6, 7].

## SUBJECTS AND METHODS

Ethics approval was obtained for this study and 12 healthy male volunteers aged 25–35 yr were recruited. None of the subjects had any known history of analgesic abuse. Each subject acted as his own control, with the two arms of the study being separated by 5 days. The study was double-blind and the subjects were allocated to groups by the pharmacist using a random number table, to receive equipotent doses of either diamorphine 4 mg or morphine 8 mg first.

An i.v. cannula with a three-way tap was inserted into a vein in the dominant hand and an infusion of 0.9% sodium chloride was started at a constant rate of 10 drops $\min^{-1}$. The subject was seated and his non-dominant arm was elevated for 1 min, at the end of which, an 8-cm band pneumatic tourniquet was inflated to a pressure of 250 mm Hg. The subject then lowered his arm to the side and was asked to support a 3-kg weight in that hand for a 2-min period to accelerate the onset of ischaemic pain. The subject indicated the development of pain in the limb by means of a visual analogue scale. This was a 10-cm strip divided into 10 sections which could be cumulatively illuminated by the subject turning a dial as the degree of pain increased. This was connected also to an oscillograph which recorded the response on paper at a speed of 25 cm $\min^{-1}$.

When the volunteer had developed a steady moderate degree of pain as reported on the visual analogue scale, the dose of either morphine or diamorphine was injected at a constant rate over 10 s via a narrow-bore tube connected to the other port of the three-way tap. The narrow tube

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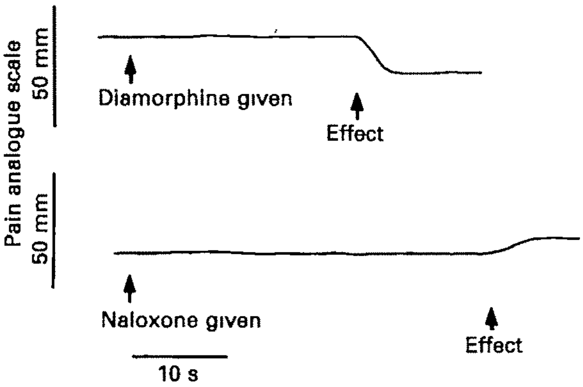

FIG. 1. Portions of a representative record showing the time of drug administration and the onset of effect, for diamorphine (upper trace) and naloxone (lower trace).

was held by the operator out of the range of vision of the subject so that he did not know when the opioid was being injected. The injection was given at a random time within 2 min of obtaining stable pain. If the subject experienced a change in the degree of pain, he adjusted the dial for the visual analogue scale appropriately. Five minutes after administration of the drug, naloxone 400 µg was injected i.v. to antagonize the effect of the opioid.

When the volunteer recorded return of pain, the study was stopped and the cuff deflated. Time from injection of opioid to relief of pain as recorded by the subject was measured from the oscilloscope trace.

The results were analysed using the Wilcoxon rank sum test.

## RESULTS

Figure 1 is an example of an oscilloscope trace, showing the method of calculating the response time for each volunteer. Figures 2 shows a comparison of the time to relief of pain after injection for morphine and diamorphine for each of the subjects. Two of the 12 subjects found diamorphine provided faster pain relief, one reported no difference and nine found morphine faster ($P < 0.01$). The median time to effect of diamorphine was 91.5 s (87.5–128.5 s, interquartile range) and the median time to effect of morphine was 59.5 (48.5–74) s.

## DISCUSSION

There are many differences between pathological and experimental pain. Pathological pain is often more severe, prolonged and has a psychological element superimposed. Nevertheless, experimental models using ischaemic limb pain as a stimulus have been developed to simulate pathological pain. Smith and colleagues [6] used a submaximal effort tourniquet technique for assessing the analgesic efficacy of differing doses of i.v. morphine [7.5–15 mg] in healthy volunteers and found it dependable.

In order to make an exact comparison of morphine and diamorphine, equipotent doses must be used. The relative potency of the agents after i.v. administration is not known. We considered that diamorphine 1 mg had a potency equal to that of morphine 2 mg on the basis of

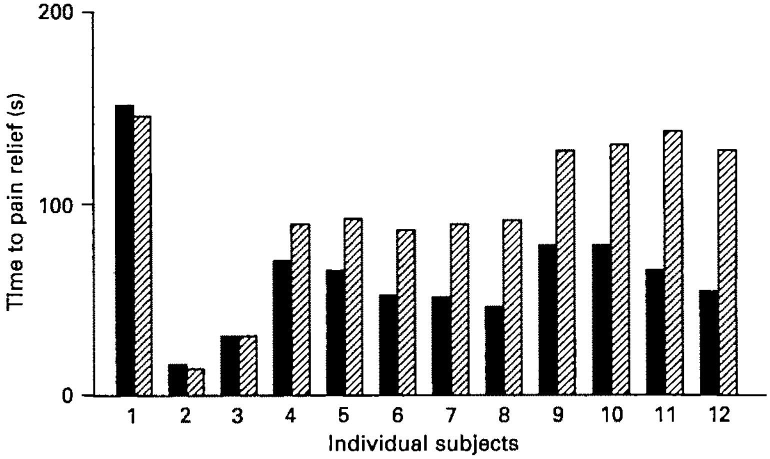

FIG. 2. Comparison of the time to onset of analgesia for morphine (■) and diamorphine (▨).

studies of i.m. administration. Kaiko and colleagues [8] found that i.m. diamorphine was twice as potent as morphine in a study comparing the analgesic and mood effects of diamorphine and morphine in cancer patients. Beaver, Schein and Hext [9] found that, when both intensity and duration of effect were considered, diamorphine was 2.4–2.6 times more potent i.m. than morphine in patients with cancer pain.

We considered the propriety of administering doses of opioids to practising anaesthetists, and chose to proceed with this as small doses, antagonized immediately under these circumstances, are most unlikely to lead to any possibility of seeking repeated administration. No subject reported a pleasant effect from administration.

Following i.m. administration, it would appear that diamorphine has a slightly earlier onset of analgesic effect than morphine [9–12]. When the drugs were given i.v., however, no difference was noted in the onset of impairment of ventilation in anaesthetized patients given morphine compared with equipotent doses of diamorphine [13]. In the present study we found that, with i.v. administration, morphine had an earlier onset of analgesic action than diamorphine. To explain this discrepancy, we must examine the factors which influence the disposition of opioids in the brain following injection.

Lipid solubility is considered an important factor in the transfer of drugs from blood to the brain. The heptane : buffer partition coefficient for diamorphine is 0.043, compared with a value of $< 0.00001$ for morphine [3–5, 14]. It might be expected, therefore, that diamorphine crosses the blood–brain barrier more readily than morphine. Plasma protein binding is another factor which may influence transfer of drug. Morphine has a lesser plasma protein binding (20 %) compared with diamorphine (40 %) [15] and therefore more morphine might be available to cross the blood–brain barrier after administration of an equipotent i.v. dose.

Both morphine and diamorphine are metabolized rapidly and some of the metabolites are pharmacologically active. Diamorphine is thought to act as a prodrug, and the metabolites 6-acetyl-morphine and morphine are responsible for the major part of its pharmacological action [16, 17]. Diamorphine is deacetylated following i.v. injection, to 6-acetyl-morphine and esterase inhibition studies suggest that this occurs quite rapidly [18]. The 6-acetyl-morphine product is less lipid soluble than diamorphine and so may cross the blood–brain barrier more slowly. *In vitro*, 6-acetyl-morphine has nine times greater affinity for brain opioid receptors than diamorphine [19]. However, when administered intracerebrally, morphine is 2–3 times more potent than either diamorphine or 6-acetyl-morphine. This suggests that diamorphine must be fully deacetylated for optimal pharmacological activity [19].

Finally, it may be that both morphine and diamorphine have some effect as a result of their metabolism to further products such as morphine-6-glucuronide. One hour after an injection of morphine, 5–10 % is found as morphine-6-glucuronide [20]. It is worthy of note that when morphine-6-glucuronide is injected into the brain, it has 5–10 times the potency of morphine and its presence in CSF after prolonged administration of morphine suggests that it makes some contribution to the analgesic effect of morphine [21].

Clearly, any evaluation of the analgesic effects of morphine and diamorphine must take account of the formation and disposition of their metabolites in the brain. The relative importance of transfer, metabolism and the potencies of the parent compounds and their metabolites are not clear. However, in clinical practice, it appears that after i.v. administration, diamorphine has no advantage in speed of action in comparison with morphine.

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# ANTAGONISM OF THE HYPNOTIC EFFECT OF MIDAZOLAM IN CHILDREN: A RANDOMIZED, DOUBLE-BLIND STUDY OF PLACEBO AND FLUMAZENIL ADMINISTERED AFTER MIDAZOLAM-INDUCED ANAESTHESIA

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W. M. S. GUNAWARDENE AND J. BACON-SHONE

## SUMMARY

*In a randomized, double-blind study, we administered placebo and flumazenil to 40 healthy Chinese boys, aged 3–12 yr, undergoing circumcision. The children received midazolam 0.5 mg kg$^{-1}$ orally for premedication and 0.5 mg kg$^{-1}$ i.v. during induction. After operation the patients were given 0.1 ml kg$^{-1}$ of a blinded solution followed by 0.05 ml kg$^{-1}$ min$^{-1}$ until either they awoke or the 10-ml ampoule of solution was empty. Efficacy of antagonism of midazolam was assessed by times to eye opening and self identification, modified Steward coma scale, a post-box toy completion-time ratio and qualitatively by an independent observer. The difference between flumazenil and placebo was both clinically and statistically different in the first 2 h. Children receiving flumazenil awoke approximately four times faster and identified themselves nearly three times sooner; 65% of this group could complete the post-box toy at 10 min, compared with none of the placebo group. There were no cases of resedation, but one child did not awaken for 30 min after i.v. administration of flumazenil 1.0 mg. The mean total dose of flumazenil administered was 0.024 (SD 0.019) mg kg$^{-1}$. Flumazenil rapidly antagonized midazolam-induced hypnosis in children and was associated with minimal change in cardiorespiratory variables.*

## KEY WORDS

*Anaesthesia: paediatric. Antagonists: flumazenil. Hypnotics, benzodiazepines. midazolam.*

The use of midazolam as an induction agent in adults and children is controversial [1–3]. A wide variability in response and difficulty in predicting an induction end-point result in large doses of midazolam (0.6 mg kg$^{-1}$) being required for reliable induction of anaesthesia in children [4, 5]. There is a consequent risk of prolonged postoperative sedation. The ability to antagonize reliably the sedative effects of midazolam would provide greater safety in the recovery room and more efficient use of the operating suite.

The dose of flumazenil required for antagonism of midazolam-induced anaesthesia and the incidence of resedation or incomplete antagonism of respiratory depression in children have not been reported previously. We modified the psychomotor post-box toy test [6] by calculating a preoperative:postoperative completion-time ratio using each patient as his own control. We then assessed efficacy of antagonism of sedation by comparing the performances in children given either flumazenil or placebo.

### PATIENTS AND METHODS

We studied 40 ASA grade I Chinese children, aged 3–12 yr, undergoing circumcision for treat-

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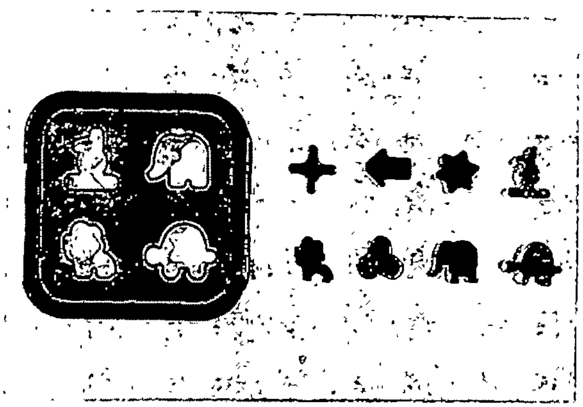

FIG. 1. The post-box toy used for psychomotor assessment.

ment of phimosis. The study was approved by the Faculty of Medicine Ethics Committee (University of Hong Kong) and written, informed consent was obtained from the parents. Children were excluded from the study if there was a history of asthma or allergies; previous adverse anaesthetic experience; halothane anaesthesia within the previous 1 month; hepatic, renal, respiratory, cardiac or haematological disease; mental retardation or age less than 3 yr.

The day before surgery, each child was familiarized with a post-box toy (fig. 1) and the completion time of his best performance on seven attempts recorded. On the day of surgery, the patient was premedicated with midazolam 0.5 mg $kg^{-1}$ (maximum dose 15 mg) and atropine 0.02 mg $kg^{-1}$ by mouth 2 h before operation. EMLA emulsion cream 2 g (lignocaine 25 mg $g^{-1}$ and prilocaine 25 mg $g^{-1}$) was applied to the dorsum of a hand. On arrival in the operating suite, the children were assessed and recorded as agitated or crying, aware and apparently anxiety free, drowsy, or asleep but responsive to command [7].

In the operating suite, a 24-gauge cannula was inserted into a vein underlying the EMLA-pretreated area. Anaesthesia was induced with midazolam 0.5 mg $kg^{-1}$ injected over 30 s. Thereafter, anaesthesia was maintained with the patient breathing spontaneously 67 % nitrous oxide and 1–3 % halothane in oxygen via a Mapleson F ($<$ 25 kg) or a Mapleson A ($>$ 25 kg) breathing system. A caudal injection of 0.25 % bupivacaine 0.5 ml $kg^{-1}$ was administered to all patients. Routine monitoring devices included an electrocardiograph, non-invasive arterial pressure recorder, pulse oximeter, capnograph and inspired oxygen concentration (Datex, Cardiocap).

The duration of anaesthesia and cardiorespiratory data during surgery were recorded. Three minutes after the child was transferred to the recovery room, he was given 0.1 ml $kg^{-1}$ of a blinded solution i.v., followed by 0.05 ml $kg^{-1}$ $min^{-1}$ until either the patient awoke or the 10-ml ampoule was empty. The blinded solution contained either flumazenil 1.0 mg in 10 ml or placebo. The volume of solution injected, time from the commencement of blinded solution injection to spontaneous eye opening and time until the patient could identify himself were recorded. During administration of the blinded solution, systolic arterial pressure, heart rate, ventilatory frequency, modified Steward coma scale [8] and a structured observation score [9] were assessed and recorded each 1 min for 10 min and subsequently at 5-min intervals until the patient awoke. Any side effects occurring during the recovery period were noted. The child's behaviour and the speed of antagonism of midazolam were considered together by an independent observer in the recovery room and were graded as excellent, good, moderate or poor.

TABLE I. *Patient, premedication and anaesthetic data (mean (SD) [range]). Statistical analysis of ordinal scale data using one-way analysis of variance and nominal scale data by chi-square analysis ($P < 0.05$ significant)*

| | Flumazenil group ($n$ = 20) | Placebo group ($n$ = 20) | $P$ |
|---|---|---|---|
| Age (yr) | 7.2 [3.5–11.5] | 6.9 [3.0–12.5] | 0.9 |
| Weight (kg) | 21.2 (5.1) [13.5–30.5] | 22.7 (6.9) [15.5–44.0] | 0.5 |
| Premedication score | | | |
| Asleep | 0 | 2 | |
| Drowsy | 0 | 0 | |
| Awake | 17 | 18 | |
| Crying | 3 | 0 | 0.02 |
| Duration anaesthesia (min) | 36 (14) [17–80] | 33 (11) [19–69] | 0.4 |

Immediately the patient became co-operative he was encouraged to complete the post-box toy in the quickest possible time. The child was offered the post-box toy at 5, 10, 30 and 60 min and 2, 4 and 18 h after operation and his fastest completion time on a single attempt recorded. The induction injection site was inspected 18 h after operation for evidence of erythema, pain or venous thrombosis.

Statistical significance ($P < 0.05$) was determined for ordinal scale data by one-way analysis of variance and for nominal scale data by chi-square analysis (with Yates' correction) using the computer interactive statistical program MINITAB [10]. Correlation was determined by calculating Spearman's rank correlation coefficient (adjusted for ties) and multivariate analysis of variance was determined using MRSP (Market Research Statistical Pack) [11].

## RESULTS

The premedication scores for the two groups were significantly different ($P < 0.02$) (table I). On arrival in the operating suite, three of the children in the flumazenil group were crying, whereas two of the placebo group were asleep but awoke on command. The mean duration of anaesthesia was 36 (SD 14) min in the flumazenil group and 33(11) min in the placebo group ($P = 0.4$) (table I).

The average dose of flumazenil administered to the children was 0.024 (0.019) mg kg$^{-1}$. Fifty-five percent of the children receiving flumazenil were given 10 ml of the blinded solution before awakening, compared with 100 % of the placebo group. Time to eye opening and self identification was significantly shorter in the flumazenil-treated patients ($P < 0.001$). The effectiveness of antagonism of anaesthesia was assessed qualitatively by a second anaesthetist as superior in all but one of the flumazenil group (fig. 2). The coma scores at 5 and 10 min were significantly greater in the flumazenil group ($P < 0.008$ and $P < 0.001$) (table II). There was a significant increase in the coma score within the flumazenil group between the 5- and 10-min assessments, but not in the placebo group ($P < 0.001$). There was a significant increase in systolic arterial pressure on awakening in the flumazenil group compared with those patients receiving placebo ($P < 0.05$), but other

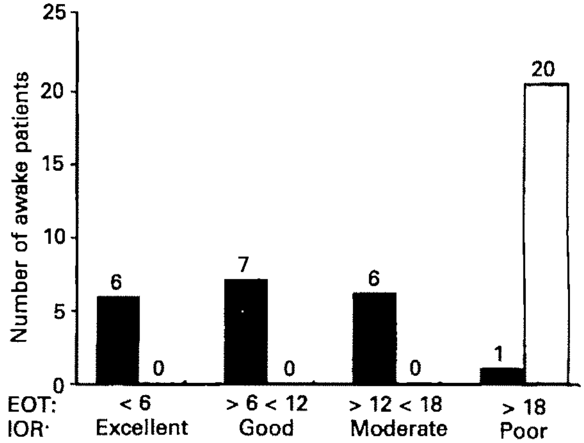

FIG. 2. Effectiveness of the antagonizing solution assessed by independent observer rating (IOR) and by eye-opening time (EOT) (Spearman's correlation $P < 0.001$). ■ = Flumazenil; □ = placebo.

TABLE II. *Awakening data (mean (SD) [range]). Statistical analysis using one-way analysis of variance (P < 0.05 significant)*

| | Flumazenil group ($n = 20$) | Placebo group ($n = 20$) | $P$ |
|---|---|---|---|
| Volume of antagonist solution administered (ml) | 8.6 (1.7) [5.0–10.0] | 10 (10) | < 0.001 |
| Time to eye-opening (min) | 10.4 (6.6) [2–32] | 37.9 (15.5) [21–76] | < 0.001 |
| Time to self-identification (min) | 17.1 (12) [6–52] | 45.1 (15.5) [22–77] | < 0.001 |
| Independent observer assessment of antagonism | | | |
| Excellent | 6 | 0 | |
| Good | 7 | 0 | |
| Moderate | 6 | 0 | |
| Poor | 1 | 20 | < 0.001 |
| Modified Steward Coma Scale | | | |
| 5 min | 4.5 (2.0) [2–9] | 1.7 (0.9) [0–4] | < 0.001 |
| 10 min | 7.4 (2.1) [3–9] | 1.9 (0.9) [0–4] | < 0.001 |

TABLE III. *Changes in cardiorespiratory data during administration of the blinded solution (mean (SD) [range]). Statistical analysis performed using one-way analysis of variance* (P < *0.05 significant*)

| | Flumazenil group (*n* = 20) | Placebo group (*n* = 20) | *P* |
|---|---|---|---|
| Ventilatory frequency (b.p.m.) | −1.2 (2.4) [−4 to 2] | −0.3 (1.6) [−4 to 2] | 0.1 |
| Systolic arterial pressure (mmHg) | 11.5 (12.7) [−11 to 35] | 2.6 (10.8) [−11 to 31] | 0.02 |
| Heart rate (beat min$^{-1}$) | 5.8 (29.4) [−44 to 66] | −5.4 (16.4) [−45 to 22] | 0.14 |

TABLE IV. *Post-box toy completion assessment (mean (SD) [range]). Statistical analysis of ordinal scale data using one-way analysis of variance and nominal scale data using chi-square analysis* (P < *0.05 significant*)

| | Flumazenil group (*n* = 20) | Placebo group (*n* = 20) | *P* |
|---|---|---|---|
| Fastest completion before op. (s) | 20 (10) [8–52] | 19 (8) [9–43] | 0.9 |
| Completion ratio after op. | | | |
| 10 min | 3.1 (0.7) [2.1–4.9] | | |
| 30 min | 2.4 (1.2) [1.4–5.9] | 16.1 (8.1) [8.0–24.2] | < 0.001 |
| 60 min | 2.2 (0.7) [1.4–3.5] | 7.4 (3.7) [2.5–14.9] | < 0.001 |
| 2 h | 2.0 (0.8) [0.9–4.0] | 2.5 (1.2) [1.4–5.6] | 0.14 |
| 4 h | 1.7 (0.6) [0.6–3.3] | 1.7 (0.6) [0.9–3.3] | 0.95 |
| 18 h | 1.3 (0.4) [0.7–2.3] | 1.3 (0.3) [0.6–1.8] | 0.8 |
| Postoperative assessment | | | |
| Toy refusal on awakening | 3 | 5 | |
| Crying on awakening | 4 | 2 | |
| Resedation | 4 | 5 | |
| Dissociated | 1 | 0 | |
| Antagonism assessed as satisfactory (%) | 65 | 0 | |

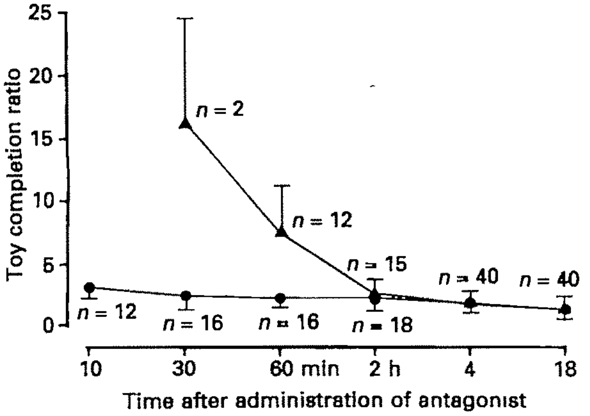

FIG. 3. Ratio of postoperative post-box toy completion-time to unmedicated practised best preoperative performance (mean, SD). *n* = Number of patients assessed. ● = Flumazenil; ▲ = placebo.

cardiorespiratory variables were similar (table III).

Psychomotor testing using a post-box toy completion-time and a ratio of best preoperative performance to postoperative completion-time was used to assess the degree of sedation (table IV). There was no difference between the two groups when comparing the fastest completion times of their best performances before operation, but the flumazenil group performed significantly better than the placebo group during the first 2 h after operation ($P < 0.02$) (fig. 3).

After operation, one child in the flumazenil group appeared dissociated for a period of approximately 3 min. An equal number of children in both groups fell asleep again after eye-opening, but all of the flumazenil-treated children were awakened easily. None of the children who received flumazenil became resedated. There were no significant differences between the placebo and flumazenil groups in relation to refusal to play with the toy or crying on awakening (table IV). There was a significant correlation between the volume of flumazenil administered and both eye-opening ($P < 0.001$) and self-identification times ($P < 0.05$). Multivariate analysis revealed no relationships of statistical significance.

## DISCUSSION

This study has demonstrated that flumazenil effectively antagonized the residual hypnotic effect of midazolam induction of anaesthesia in children. All aspects of arousal assessment during the first 2 h after operation demonstrated that flumazenil was superior to placebo. The mean dose of flumazenil required to antagonize the effects of midazolam was 0.024 mg $kg^{-1}$. The dose of flumazenil reported to awaken adult patients in whom midazolam was used to induce anaesthesia was approximately 0.5 mg [12–14]. In our children, the dose administered ranged from 0.5 to 1.0 mg, and 55 % of the flumazenil group were given a maximum dose of 1.0 mg before awakening. Despite the relatively large dose per kilogram of midazolam (0.5 mg $kg^{-1}$) used to induce anaesthesia in our children, antagonism was achieved with a dose of flumazenil similar to that given to adults. However, there was only a weakly significant relationship between body weight and the dose of flumazenil required for awakening ($P < 0.04$) and this showed no correlation with age.

The onset and mode of action of midazolam depend in part on the relationship between the benzodiazepine receptor and the gamma-aminobutyric acid (GABA)–receptor complex [15]. It has been demonstrated that the rate of chloride uptake by cultured neurones after administration of midazolam is dose-dependent [16]. The onset of anaesthesia with midazolam is faster in children [4] and this may be a result of greater free midazolam concentration around the benzodiazepine receptor or a stronger affinity of midazolam for the benzodiazepine receptor. Flumazenil antagonism of benzodiazepine effects depends on the number of receptors occupied at the time of administration of flumazenil [17]. It is surprising that there was no demonstrable relationship between the doses of midazolam and flumazenil. It is postulated that the hypnotic effects of benzodiazepines occur with 60–90 % receptor occupancy and anxiolytic properties at 20–30 % receptor occupancy [18]. Large doses of midazolam are necessary for hypnosis, but small doses of flumazenil convert the adult from the hypnotic to the sedated state [18]. The variable response to midazolam and dose requirement of flumazenil in relation to body weight in children requires further investigation. Children may differ from adults in their pharmacokinetic profile, plasma protein binding, receptor occupancy rate, chloride channel opening frequency and the amount of GABA present at the GABA receptor [16].

Mean eye-opening and self-identification times were approximately three times faster in the flumazenil group. One child in this group did not awaken for 30 min after flumazenil and behaved in a manner identical to the placebo group. This may have been caused by undue sensitivity to midazolam, resistance to flumazenil, unusual pharmacokinetic profile of these drugs or the unlikely event of there not being any active drug in that particular ampoule of blinded solution. The remaining flumazenil-treated children awoke within 18 min of administration, while the placebo-treated group demonstrated a wide variation in awakening times (20–77 min). The modified Steward coma scales at 5 and 10 min were statistically and clinically superior in the flumazenil-treated children. These children demonstrated a rapid regaining of consciousness and airway control compared with the placebo group, who required vigilant observation for a long period.

The observer assessed both the rate and quality of antagonism (table II). The flumazenil-treated children awakened faster and they were also more co-operative, more rapidly calmed if distressed and, if they went back to sleep, they were easily aroused. Resedation after antagonism of midazolam in our children did not present the same problem as in adults [19]. This may be because they were given a single i.v. dose of midazolam, lack of concomitant disease and absence of synergistic drugs (excluding halothane) for supplementation of anaesthesia. Interestingly, Geller and colleagues found that, although flumazenil did not antagonize halothane anaesthesia, it had a definite effect on hastening recovery, in addition to making it more pleasant [20]. Antagonism of the midazolam-induced deep hypnosis by careful titration of flumazenil appears to leave the anxiolytic properties of midazolam intact [21]. The placebo group had a greater rate of refusal to perform the toy test, were irritable on awakening and were still somnolent after eye-opening. One child awoke after administration of flumazenil and remained uncommunicative and in a dissociated state for about 3 min. The child then began to cry and appeared normal.

Vomiting, tremor and involuntary movements reported in adults after administration of flumazenil [15], were not seen in any of our children. The low incidence of vomiting may be explained by the brief duration of anaesthesia, the midazolam premedication and the use of caudal analgesia rather than opioids.

The post-box toy completion-time ratio provided a sensitive psychomotor assessment and a measure of the speed of recovery from anaesthetic agents, which we believe is independent of the practice effect of complex motor skills. During the first 2 h after operation, the flumazenil group performed significantly faster compared with the placebo-treated children. This is in accord with previous clinical experience in adults [22, 23] and the pharmacokinetic profiles of midazolam and flumazenil [24, 25]. At 4 h the mean toy completion-time ratios were identical between the two patient groups and their performance was less than twice their preoperative, practised, unmedicated, fasted completion time. Despite the large dose of midazolam given at premedication and induction of anaesthesia, both the flumazenil-treated and placebo-treated children demonstrated a degree of recovery from anaesthesia which would allow them to be safely discharged home 4 h after operation.

The mean change in cardiorespiratory variables compared with values before administration of the antagonist were small and similar in both groups. The only statistically significant finding was a small increase in systolic arterial pressure after flumazenil, corresponding to normal awakening—a finding similar to that of Geller and colleagues in adults [26].

## ACKNOWLEDGEMENT

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# COMPUTERIZED DYNAMIC POSTUROGRAPHY: A NEW METHOD FOR THE EVALUATION OF POSTURAL STABILITY FOLLOWING ANAESTHESIA

A. GUPTA, T. LEDIN, L. E. LARSEN, C. LENNMARKEN AND L. M. ÖDKVIST

## SUMMARY

*Dynamic posturography, a new method to study postural stability in humans, was performed in 11 healthy volunteers before administration of midazolam 0.1 mg/kg body weight i.v., and repeated subsequently at 45, 105 and 165 min. Results indicate that balance was affected significantly (*$P < 0.008$*) up to 45 min after i.v. midazolam and did not return to control values until 105 min. The quantified version of the Romberg test performed with the eyes open or closed using the Equitest did not appear to be sensitive in detecting residual effects of midazolam on balance. We conclude that healthy, young persons should not be considered to have regained postural stability for up to 105 min after sedation with midazolam. Dynamic posturography appears to be a useful test in the objective assessment of balance disturbances.*

**KEY WORDS**

*Recovery. Hypnotics, benzodiazepines: midazolam. Measurement techniques: dynamic posturography*

There has been a rapid increase in the number of operations being performed on a day-case basis over the past few years [1]. Rapid recovery after anaesthesia or sedation is an important factor to be considered when choosing a safe anaesthetic for outpatient surgery. Consequently, short acting drugs such as midazolam and propofol are used commonly for sedation.

The ability to maintain postural stability is an important factor in the assessment of recovery and "street fitness". However, standardized tests for assessment of balance are not available. Simple clinical tests (Romberg test or the ability to walk) do not seem adequate for deciding on the safe discharge of patients after outpatient surgery [2, 3]. Static posturography, or the quantitative assessment of human stability, has been used in measurement of recovery from anaesthesia [4, 5]. An instrumented force platform which measures body sway was described by Korttila [6]. This was found to be sensitive to detect balance disturbances after thiopentone, diazepam and methohexitone anaesthesia, and clinically useful, as data could be analysed immediately [7]. Computerized dynamic posturography [8, 9] is a new method for assessing human balance and posture, and has been used extensively in clinical practice for assessing and differentiating disturbances of vestibular, visual and proprioceptive functions, and central co-ordination. It has not been used, to our knowledge, for detection of balance disturbances after anaesthesia and sedation. We have used this test in assessing recovery from the effect of sedative medication in healthy volunteers.

## SUBJECTS AND METHODS

The study was approved by the University Ethics Committee. Informed consent was obtained from 11 ASA I subjects aged 23–36 yr. No subject was taking any medication likely to affect postural stability. No food or drink was allowed for 6 h before the study. The subjects were asked to refrain from drinking alcohol or taking any

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medicine for 24 h before the test period. The test procedure was explained before control values were obtained on the computerized dynamic posturography apparatus (Equitest, Neurocom International Inc., Clackamas, Oregon, U.S.A.).

A cannula was inserted into a vein on the dorsum of the non-dominant hand for injecting drugs. Midazolam 0.1 mg/kg body weight was injected over 1 min and any adverse effects were recorded. The subjects were allowed to rest before further recordings were made at 45, 105 and 165 min after injection of midazolam. Variables monitored included arterial pressure, ECG, heart rate and ventilatory frequency.

*Computerized dynamic posturography* was performed as described by Cyr, Moore and Möller [8] and Nashner [9]. The subject stands on a dual forceplate enclosed by a visual surround. Both the forceplate and the visual surround can be made to move with the individual's antero–posterior sway or independent of sway, thus enabling programmed disturbances of equilibrium. The dual forceplate records the vertical forces between the feet and ground in addition to horizontal antero–posterior shear forces, thereby allowing estimation of the position of the swaying body and the pattern of sway in terms of hip or ankle strategy for correcting these disturbances. Vertical force transducers are located in all four quadrants of the dual forceplate. The shear force transducer is positioned in the middle of the dual forceplate.

The Equitest can be used to test two main components: *sensory organization* (SO) and *movement co-ordination* (MC), but we have tested only the former. The software for the latter is still in the process of development [Neurocom Inc., personal communication]. The sensory portion of the test battery varies visual and proprioceptive inputs while determining the effect on equilibrium. For the effect of sensory system manipulation to be interpreted accurately, an intact motor system must be present. The SO part is divided into six separate testing conditions lasting 20 s each. SO1 is a quantified version of the Romberg test. The subject stands with eyes open and the surrounding and the support surface are stable. As all three sensory systems are operational, a high equilibrium score (defined below) should be obtained. SO2 is equal to SO1 except that the eyes are closed. Again, a high equilibrium score should be obtained because the absence of visual cues has little effect on balance in normal subjects in whom the vestibular and proprioceptive systems are functional. In SO3, performed with the eyes open, the surrounding moves in response to body sway, thus the visual cues are distorted. Under this condition, the brain is asked to ignore the inaccurate visual inputs. Because the person's stance is fairly wide-based, equilibrium should remain fairly normal under this condition, particularly if the vestibular system is normal. In test SO4, the platform is sway referenced, and the surrounding stable. As a result, the proprioceptive input to the brain is inaccurate, and balance must be maintained by the visual and vestibular systems. In test SO5, with the eyes closed, the platform is sway referenced, and thus the proprioceptive system is compromised and the visual system is eliminated and only one of the three sensory systems is fully operational. Equilibrium and balance must then, to a great degree, be maintained by the vestibular system alone. In test SO6, both the platform and the surrounding are sway referenced. Under this condition, both vision and proprioception are compromised. Tests SO3–SO6 are repeated to get more stable values. Note that in SO3 and SO6 the subject might have some orientation information from the surrounding, as it is moving only in the antero–posterior direction and not in the lateral direction.

From each test an *equilibrium score* is computed by calculating the angle between the swaying body and earth vertical. The score is 100 for absolutely no sway, decreasing with increasing sway range, and zero for 12.5° sway range or in case of a fall. A *strategy score* is also computed, related to the amount of shear force exerted, expressing the degree of ankle or hip movements: 100 = solely ankle and no hip movements; 0 = hip movement generating approximately 110 N shear force. The subjects are secured to the apparatus by a safety harness to prevent falling.

### *Statistics*

Paired Student's $t$ test was used to examine if the differences between the scores before and after the injection of midazolam were statistically significant. Baseline values were taken at 0 min and all subsequent results were compared with these values. The Bonferroni correction was applied in order to reduce the consequent increased probability of Type 1 error because of six different tests being performed at each time interval. A significant level of 0.05 was thus divided by six to yield a significance level of 0.008 ($P < 0.008$).

TABLE I. *Mean* (SD) *equilibrium scores* (%) *for the six conditions* (*SO1–SO6*) *studied, computed by calculating the angle between the swaying body and earth vertical. 100 % = absolutely no sway, decreasing with increasing sway range; 0 % = 12.5° sway range or a fall. Time 0 min = control values before the injection of midazolam; 45, 105 and 165 min = after injection of midazolam. Bonferroni correction was applied and* P < *0.008 was considered statistically significant* (*)

| | Equilibrium score (%) | | | |
|---|---|---|---|---|
| Condition | 0 min | 45 min | 105 min | 165 min |
| SO1 | 95.8 (2.8) | 87.5 (10.3) | 93.5 (3.6) | 94.9 (3.6) |
| *P* | | < 0.019 | < 0.12 | < 0.29 |
| SO2 | 93.2 (1.7) | 78.2 (22.6) | 87.6 (6.8) | 91.1 (4.0) |
| *P* | | < 0.44 | < 0.014 | < 0.36 |
| SO3 | 92.0 (3.4) | 74.8 (27.1) | 89 (5.8) | 91.7 (2.3) |
| *P* | | < 0.053 | < 0.16 | < 0.77 |
| SO4 | 90.3 (5.3) | 69.8 (26.1) | 86.6 (8.3) | 90.9 (4.0) |
| *P* | | < 0.015 | < 0.10 | < 0.18 |
| SO5 | 72.1 (0.3) | 41.5 (34.4) | 66.7 (15.4) | 68.7 (10.6) |
| *P* | | < 0.007* | < 0.25 | < 0.91 |
| SO6 | 72.1 (12.0) | 48.6 (29.7) | 66.6 (16.8) | 68.4 (13.8) |
| *P* | | < 0.006* | < 0.25 | < 0.68 |

TABLE II. *Mean* (SD) *strategy scores for the six conditions* (*SO1–SO6*) *studied. Strategy score is related to the amount of shear force exerted, expressing the degree of ankle or hip movement: 100 = solely ankle and no hip movements; 0 = hip movement generating approximately 110 N shear force. Time 0 min = control values before the injection of midazolam; 45, 105 and 165 min = after injection of midazolam. Bonferroni correction was applied and* P < *0.008 was considered statistically significant* (*)

| | Strategy score | | | |
|---|---|---|---|---|
| Condition | 0 min | 45 min | 105 min | 165 min |
| SO1 | 98.2 (1.8) | 98.1 (2.4) | 98.9 (0.8) | 99.0 (0.6) |
| *P* | | < 0.92 | < 0.32 | < 0.46 |
| SO2 | 98.0 (1.5) | 91.6 (15.9) | 94.3 (11.1) | 97.9 (1.3) |
| *P* | | < 0.20 | < 0.29 | < 0.82 |
| SO3 | 98.0 (1.3) | 97.0 (2 1) | 97.1 (3.9) | 97.9 (1.6) |
| *P* | | < 0.26 | < 0.51 | < 0.89 |
| SO4 | 91.4 (3.4) | 87.1 (6.0) | 89.9 (3.0) | 92.4 (1.7) |
| *P* | | < 0.003* | < 0.17 | < 0.07 |
| SO5 | 82.7 (5.6) | 79.5 (7.9) | 83.9 (5.5) | 82.3 (6.9) |
| *P* | | < 0.08 | < 0.49 | < 0.60 |
| SO6 | 85.5 (4.8) | 79.5 (14.9) | 84.5 (4.4) | 85.6 (4.5) |
| *P* | | < 0.11 | < 0.31 | < 0.19 |

## RESULTS

All the subjects (seven male, four female) were within the normal range for the normative data representative of their age group as calculated by Neurocom International Inc.: mean age 29.2 yr (range 23–36 yr); mean weight 73.2 (SD 11.7) kg (range 57–93 kg); mean height 180.1 (SD 9.8) cm (range 170–195 cm).

Mean (SD) equilibrium scores in the sensory conditions SO5 and SO6 were significantly different 45 min after i.v. midazolam (table I). However, all the equilibrium scores had returned to control values at 105 min.

Mean (SD) of the strategy scores are shown in table II. There was no significant change in equilibrium strategy in any of the conditions tested except condition SO4 at 45 min where hip, rather than ankle strategy was used to correct body position.

One person fell on all the conditions at 45 min. Five of 11 subjects fell on condition SO5 at 45 min and three fell on condition SO6 at 45 min.

Arterial pressure, heart rate, ECG and ventilatory frequency remained stable throughout the procedure. No person complained of nausea or vomited during the period under study and no subject complained of double vision during or after the test period.

All persons were fully awake and could answer questions accurately 105 min after the injection of midazolam. Four of the 11 subjects were slightly tired the same evening, although all of them walked or cycled home after the test period (elicited by a questionnaire sent to all the participants a few days later).

## DISCUSSION

This study has demonstrated that midazolam 0.1 mg $kg^{-1}$ given i.v. to 11 healthy volunteers caused disorders of balance up to 45 min later, and that balance had not returned to control values until 105 min.

In order to remain in standing equilibrium, postural muscles generate acceleration forces acting upon the body segments. The cerebellum and the brainstem integrate signals from the somatosensory, visual and vestibular systems and correct equilibrium disturbances. These three systems contribute to postural control, and damage to any of them, or to the brainstem or cerebellum, influences the overall output of the postural system; this may be studied by posturography.

In clinical practice, the Romberg test is often used to assess ability to maintain balance. However, it is not objective and therefore it is very difficult, if not impossible, to grade the degree of imbalance by observation. This test appears, therefore, to be inadequate as a guideline for the safe discharge of patients after ambulatory surgery [2, 3]. Walking on a straight line suffers the same limitations as the Romberg test. Korttila used both these tests, together with other clinical tests of recovery, and compared them with psychomotor test batteries in volunteers after sedation with diazepam [10]. He observed that these tests showed no impairment of performance 30 and 150 min after injection, whereas the psychomotor tests revealed considerable impairment of reactive and co-ordinative skills.

The classical way of estimating liability to fall is that of spontaneous sway measurements on a stable platform (static posturography) in standing man [11]. Measurements in static posturography do not resemble the dynamic conditions that characterize daily life. Falls are not likely to occur in stable standing, but occur usually in situations of unexpected equilibrium disturbances, which require fast corrections of body position, demanding both muscular strength and adequate muscle co-ordination. Increased spontaneous sway is, however, not an entirely successful predictor in identifying individuals at risk of falling, particularly in the older age group [12]. Balance testing would benefit, therefore, from a more dynamic measurement situation. Dynamic posturography is a new investigation procedure that enhances measurement of spontaneous sway by exposing the subject to conditions in which the surround and the support platform can be made to follow the sway, increasing the difficulties of correcting disturbances of equilibrium. By making the visual surround and the support surface stable or sway-referenced, it is possible to test the different inputs to the postural system separately and accurately. This method has been shown previously to be very sensitive in detecting influences on balance functions during exercise in the elderly [13] and equilibrium abnormalities in acute alcoholic intoxication [14].

In this study, midazolam 0.1 mg $kg^{-1}$ i.v. resulted in significant abnormality in the sensory organization conditions SO5 and SO6 at 45 min. At 105 min, all components of this test had returned to control values. One earlier study [15] examined the problem of balance disturbances after sedation with midazolam and diazepam using the Romberg test and the ability to walk on a straight line. In that study, balance was disturbed up to 120 min after midazolam, but only up to 60 min after diazepam. This contrasts with our findings which suggest that balance had returned to normal within 105 min after i.v. midazolam. The quantitative version of the Romberg test with the eyes open and closed (conditions SO1 and SO2) at 45 min did not show any difference from control values, suggesting that it is an insensitive test for the detection of postural stability after sedation with midazolam. This difference in findings between the previous study and ours could be because the Romberg test is very subjective and hence difficult to interpret.

The plasma half-life of midazolam is approximately 120 min [16] and it has an effective duration of action varying from 90 to 240 min. This wide variation in duration of action may be a reflection of interindividual variation and of the different methods used to assess recovery.

The instrumented force platform was used by Korttila and others [6] to study static posturography after thiopentone, methohexitone and diazepam i.v. Results suggested that there was no significant body sway after methohexitone compared with normal saline. However, thiopentone was associated with increased sway up to 1 h later and diazepam up to 7 h. Closer examination of this study shows that, although patients given diazepam had returned to control sway values at 5 h, they had increased sway at 7 h. This could be because of the phenomenon of resedation, which has been described previously for midazolam [17]. Our results on dynamic posturography using midazolam did not appear to show this, although investigations were performed for only up to 165 min after i.v. injection.

Double vision, a common complication of anaesthesia, does not appear to be a problem with midazolam sedation. This is supported by the facts that, not only did none of our volunteers experience this, but also, if it were present, condition SO1 (which is a quantified version of the Romberg test with the eyes open) would also have been likely to show significant differences at 45 min.

Under normal standing conditions, most people use the ankle joint as a fixed point. This is referred to as ankle strategy. When body sway is increased beyond that which the ankle strategy can manage, the individual must incorporate corrective movements by bending at the hip. In normal healthy persons, hip strategy is considered inappropriate for the degree of body sway induced by the conditions SO1–SO4 tested here. However, because conditions SO5 and SO6 test the balance system to its extremes, hip strategy is not uncommon in these conditions alone. Thus ankle strategy is the primary strategy of corrective movement in case of body sway during simple standing conditions. Our study failed to show any significant effects of midazolam on equilibrium strategy except in condition SO4 at 45 min where hip, rather than ankle strategy was used to correct body position.

In summary, the Equitest seems to be a useful advance in the study of balance disturbances after sedation. Conditions SO5 and SO6 which strain the balance system to an extreme are, perhaps, the most sensitive in the detection of postural abnormalities.

Volunteers given i.v. midazolam had returned to baseline sway values after 105 min and may be considered to possess adequate postural stability to maintain balance. Thus dynamic posturography seems to be a useful method to study balance disturbances after anaesthesia and sedation.

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# DOSE-RELATED EFFECTS OF ISOFLURANE ASSOCIATED WITH LOW PLASMA CONCENTRATIONS OF VERAPAMIL ON GLOBAL AND REGIONAL FUNCTION IN NORMAL AND COMPROMISED CANINE MYOCARDIUM

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## SUMMARY

*Global and regional myocardial functions were studied in seven open-chest dogs with constant low plasma concentrations of verapamil as increasing concentrations of isoflurane (0.75, 1, 1.5 MAC) were administered in the presence of normal myocardial perfusion and after application of critical constriction of the left anterior descending coronary artery. In the presence of verapamil, increases in isoflurane concentrations caused dose-dependent myocardial depression both before and after critical coronary constriction. The systemic and coronary vasodilatation associated with high concentrations of isoflurane did not occur in the presence of verapamil. The association of verapamil with isoflurane caused regional myocardial dysfunction that worsened at high isoflurane concentrations. This regional dysfunction could not be antagonized in two dogs. The effects of isoflurane on regional function were not modified by application of a critical coronary constriction.*

***KEY WORDS***

*Anaesthetics, volatile: isoflurane. Heart: myocardial function, ischaemia, verapamil*

As increasing numbers of patients are being treated with calcium antagonists, it is important to determine the effects of inhalation anaesthetics in the presence of calcium channel block. This association has been studied extensively with reference to myocardial depression [1–6]. We have reported previously the occurrence of regional myocardial dysfunction when verapamil was administered during halothane or isoflurane anaesthesia [7, 8] when coronary blood flow and coronary perfusion pressure were maintained at values unlikely to cause transmural ischaemia. As calcium antagonists are used in patients suffering from ischaemic heart disease, we wondered if regional dysfunction caused by the association of verapamil with increasing concentrations of isoflurane might worsen under experimental conditions of compromised coronary perfusion induced by critical coronary artery constriction.

## MATERIALS AND METHODS

Seven mongrel dogs weighing 15–21 kg were premedicated with morphine 1 mg kg$^{-1}$ i.m. Anaesthesia was induced with thiopentone 10 mg kg$^{-1}$, the trachea was intubated, and the lungs ventilated by constant volume intermittent positive pressure with 66% nitrogen in oxygen; carbon dioxide was added to maintain normocapnia. During surgical preparation, an-

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aesthesia was maintained with halothane. Temperature (mid-oesophagus) was maintained at 37–38 °C by a heating element incorporated into the operating table.

An i.v. cannula was inserted into the femoral vein for infusion of 0.9 % saline at a constant rate of 4 ml $kg^{-1}$ $h^{-1}$, and a rigid 9-French gauge polyethylene catheter was inserted into the left common carotid artery and advanced to within 1 cm of the aortic valve for measurement of systemic arterial pressure (Statham P23De pressure transducer).

A left thoracotomy was performed, the fifth and the sixth ribs excised, and the heart exposed and suspended in a pericardial cradle. A cannula was inserted into the pulmonary artery via the outflow tract of the right ventricle for measurements of cardiac output (dye dilution), and a rigid 9-French gauge cannula was inserted into the left ventricle via a stab wound in the apical dimple for measurement of pressure (Statham P23De pressure transducer).

The aortic root was dissected free of its fat pad, and an appropriately sized electromagnetic flow transducer (SEM 230, SE Laboratories, Feltham, U.K.) was placed around it. The left anterior descending coronary artery (LAD) was dissected free distal to the second major diagonal branch, and an electromagnetic flow transducer (SEM 230, SE Laboratories) was placed around it. Two pairs of ultrasonic piezo-electric crystals were inserted at the level of the subendocardium, parallel to the short axis of the heart. One pair was implanted in the apical area supplied by the left descending coronary artery (LAD), and the other in the upper part of the free wall of the left ventricle supplied by the left circumflex coronary artery (LC).

Regional myocardial function was assessed by continuous measurement of segmental length between each pair of crystals, based on the transit time of ultrasound. The transit time signal was converted into a length signal as ultrasound travels through the myocardium at a constant velocity of 1.56 mm $\mu s^{-1}$ [9, 10].

Regional dimensions were measured as follows: end-diastolic length (EDL) was measured at the time of the beginning of the sharp upslope of the first derivative of the left ventricular pressure (LV$dP/dt$) signal; end-systolic length (ESL) was measured at the time of closure of the aortic valve, as indicated by the time when the aortic blood flow first returns to zero; maximum length ($L$max), minimum length during systole ($L\mathrm{min}_S$) and minimum length during diastole ($L\mathrm{min}_D$) were also measured. Percentage of systolic and post-systolic shortening (%SS and %PSS) were calculated as follows:

$$\%SS = [(EDL - L\mathrm{min}_S)/EDL] \times 100$$

$$\%PSS = [(ESL - L\mathrm{min}_D)/(L\mathrm{max} - L\mathrm{min}_D)] \times 100$$

In a normal segment, $L\mathrm{min}_S$ occurs at the end of systole and $L$max occurs at the end of diastole. However, in abnormal segments, $L$min may occur during diastole ($L\mathrm{min}_D$). Similarly, an increase in length may develop after aortic valve opening, in which case there is systolic bulge. The simultaneous recording of left ventricular (LV) pressure and regional dimensions makes it possible to examine their time course and to obtain pressure–length loops [8].

The time of onset of regional shortening and lengthening was measured with reference to the time when the LV$dP/dt$ signal reached 200 mm Hg $s^{-1}$.

ECG (lead II), PR interval, aortic and LV pressures, aortic flow and aortic blood acceleration (differentiation of the flow signal) were recorded simultaneously, together with the length signals. Stroke volume was obtained by on-line integration of the flow signal, and was calibrated by triplicate determination of cardiac output by dye dilution.

Derived haemodynamic variables were calculated using conventional formulae.

Coronary perfusion pressure (CPP) was calculated by subtracting left ventricular end-diastolic pressure (LVEDP) from aortic diastolic pressure, and effective coronary vascular resistance (CVR) was calculated by dividing CPP by mean coronary blood flow (CBF).

The signals were recorded on a Mingograph 81 eight-channel recorder (Elema Schonander, Stockholm, Sweden) at a paper speed of 250 mm $s^{-1}$. As an index of early global diastolic function, the time constant of isovolumic relaxation ($T$relax) was calculated [11]. This was achieved by regression analysis of the logarithm of the instantaneous values of pressure against time, for the period from aortic valve closure to the time when LV pressure reached 10 mm Hg greater than LVEDP.

Blood samples for measurement of plasma concentration of verapamil by high-pressure liquid chromatography [12] were obtained at the end of the loading dose and at 30 and 90 min after the start of the constant infusion.

After the surgical preparation was completed, halothane was replaced by isoflurane, delivered by a Cyprane vaporizer calibrated by mass spectrometry. Blood-gas tensions were measured and, where necessary, ventilation adjusted to ensure normocapnia, and sodium bicarbonate given to correct any metabolic acidosis. One hour after isoflurane 0.75 MAC had been introduced to replace halothane, verapamil was given i.v. as a loading dose of 250 $\mu g\ kg^{-1}$ over 30 min, followed by a maintenance dose of 60 $\mu g\ kg^{-1}\ h^{-1}$. Note that surgery had been completed, and that for the duration of the study the animals did not breathe spontaneously or move, although neuromuscular blockers were not administered. Recordings were obtained at 0.75 MAC isoflurane 30 min after beginning the maintenance dose of verapamil. Isoflurane concentration was increased to 1 MAC for 15 min and its effects recorded before increasing it to 1.5 MAC for another 15 min. Control measurement (0.75 MAC isoflurane) were obtained 30 min after the isoflurane concentration had been reduced. Critical constriction of the LAD was applied, as described previously [13–15]. Twenty minutes after a satisfactory and stable critical stenosis had been obtained, the same incremental concentrations of isoflurane were applied and the effects recorded after 15 min for each concentration.

Differences between values for successive concentrations of isoflurane were analysed by two-way analysis of variance followed by Duncan's multiple range test. Differences between normal and impaired coronary perfusion data were analysed using paired Student's $t$ tests.

## RESULTS

Mean (SD) plasma concentrations of verapamil were 69 (21) ng $ml^{-1}$ at the end of the loading dose, 46 (11) ng $ml^{-1}$ 30 min and 50 (11) ng $ml^{-1}$ 90 min after the beginning of the maintenance infusion. Norverapamil was not detectable in these samples.

Haemodynamic data are shown in table I. Increasing the isoflurane concentration did not change heart rate and PR interval. A dose-related depression of arterial pressure and all indices of global cardiac performance occurred with increases in isoflurane concentration, with maximal decreases of 30% for aortic blood acceleration, 51% for left ventricular stroke work, 45% for left ventricular peak power and 32% for LV$dP/dt_{max}$. Cardiac output and stroke volume decreased in a dose-dependent fashion, by 34% and 34.5%, respectively. LVEDP increased at 1.5 MAC isoflurane, while systemic vascular resistance remained unchanged. Relaxation was impaired as indicated by increases in $T$relax (30%) and decreases of negative LV$dP/dt$ max (−39%). CBF (−32%) and CPP (−33.5%) decreased significantly, while effective CVR remained unchanged with increasing concentrations of isoflurane. The reduction in CBF was similar to that in CPP (fig. 1).

Data on regional function are displayed in table II. A slight increase in EDL occurred in both basal and apical regions, reaching significance only in the basal region. A dose-related depression of systolic shortening occurred in both regions. Abnormal wall motion was present in both regions, but increased significantly only in the LAD territory, where post-systolic shortening represented 47% of total shortening at 1.5 MAC isoflurane. An example of pressure–length loops (fig. 2) shows the increases in PSS and systolic bulging in response to increasing isoflurane concentration from 0.75 to 1.5 MAC.

Only five of the dogs were submitted to critical coronary constriction as, in the other two, regional function was considered to have recovered incompletely from the greatest concentration of

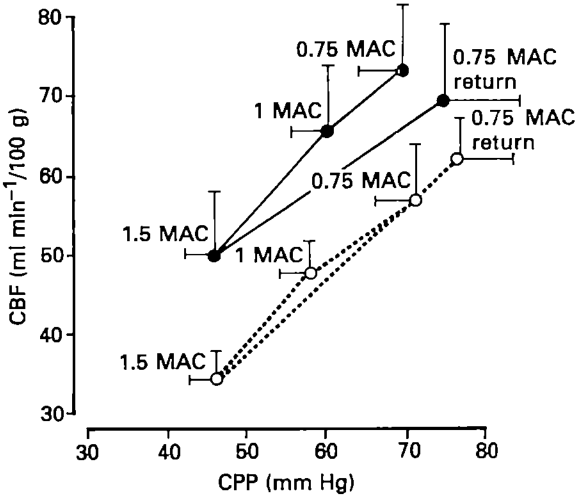

FIG. 1. Relationship between coronary blood flow (CBF) and coronary perfusion pressure (CPP) at three concentrations of isoflurane, before ($n = 7$, bold lines) and after ($n = 5$ broken lines) critical coronary artery constriction. Bars represent SEM.

TABLE I. *Effects on haemodynamic state of increasing concentrations of isoflurane associated with a low dose of verapamil before and after application of critical constriction to the LAD coronary artery (mean* (SEM)).† *0.75 MAC return. MAP = Mean arterial pressure; LVEDP = left ventricular end-diastolic pressure; CO = cardiac output; LV = left ventricular; SVR = systemic vascular resistance; Neg. = negative; CPP = coronary perfusion pressure; CVR = coronary vascular resistance; CBF = coronary blood flow; CI = cardiac index.* **$P < 0.05$ (analysis of variance followed by Duncan's multiple range test)*

| | Before critical constriction | | | | After critical constriction | | | |
|---|---|---|---|---|---|---|---|---|
| Isoflurane MAC: | 0.75 | 1 | 1.5 | 0.75R† | 0.75 | 1 | 1.5 | 0.75R† |
| Heart rate (beat $min^{-1}$) | 120 (4.5) | 122 (3.8) | 122.5 (3.9) | 122 (6.4) | 122.5 (10.2) | 130 (5.7) | 130 (3.9) | 132 (9) |
| MAP (mm Hg) | 90.0 (5.9) | 77.6 (5.0)* | 66.4 (5.2)* | 97.2 (6.6) | 86.7 (5) | 72.7 (3.7)* | 61.3 (3)* | 92.4 (7.5) |
| LVEDP (mm Hg) | 5.9 (0.3) | 5.6 (0.3) | 7.35 (0.7)* | 5.5 (0.5) | 5.3 (0.3) | 5.4 (0.7) | 6.8 (1.2) | 6 (0.9) |
| Stroke volume (ml $kg^{-1}$) | 0.95 (0.08) | 0.81 (0.08)* | 0.62 (0.07)* | 0.93 (0.1) | 0.89 (0.09) | 0.77 (0.03)* | 0.60 (0.04)* | 0.87 (0.08) |
| CO index (ml $min^{-1}$ $kg^{-1}$) | 113 (9) | 97 (7)* | 75 (7)* | 109 (7) | 106 (6) | 100 (6) | 79 (6)* | 114 (12) |
| Aortic blood acceleration (ml $s^{-2}$) | 4320 (480) | 3770 (450)* | 3000 (350)* | 4330 (440) | 4340 (610) | 3630 (450)* | 2690 (350)* | 4100 (440) |
| LV stroke work (mJ) | 11.4 (1.2) | 8.5 (1)* | 5.6 (1)* | 11.8 (1.2) | 10.2 (0.9) | 7.5 (0.3)* | 4.9 (0.4)* | 10.4 (0.8) |
| LV peak power (mW) | 2580 (300) | 1990 (290)* | 1410 (240)* | 2690 (300) | 2300 (230) | 1750 (130)* | 1200 (190)* | 2450 (190) |
| LV$dP/dt_{max}$ (mm Hg $s^{-1}$) | 1300 (120) | 1080 (90)* | 870 (60)* | 1320 (120) | 1320 (200) | 1080 (150)* | 860 (100)* | 1410 (190) |
| SVR (dyn s $cm^{-5}$) | 3300 (280) | 3300 (300) | 3800 (450) | 3670 (350) | 3350 (460) | 2970 (370) | 3230 (490) | 3410 (590) |
| Neg. LV$dP/dt$ (mm Hg $s^{-1}$) | 1650 (140) | 1400 (125)* | 1000 (100)* | 1830 (150) | 1830 (190) | 1430 (140)* | 970 (110)* | 1950 (200) |
| *T*relax (ms) | 33.2 (1.6) | 36.6 (1.9)* | 43.2 (2.6)* | 34.1 (3) | 29.9 (2.3) | 33.2 (4.6)* | 41.5 (5.2)* | 29.4 (3.1) |
| LAD blood flow (ml $min^{-1}$/100 g) | 73.2 (8.1) | 65.4 (8.2) | 49.7 (7.4)* | 69.2 (9.4) | 56.7 (7) | 47.6 (3.9)* | 34.3 (3.8)* | 62.6 (2.7) |
| CPP (mm Hg) | 69.5 (5) | 60.6 (4.3)* | 46.2 (3.8)* | 74.8 (8.7) | 71.3 (5.3) | 57.8 (3.6)* | 46.2 (3)* | 76.4 (7.6) |
| CVR (mm Hg $min^{-1}$/100 g) | 1.012 (0.107) | 1.082 (0.235) | 1.103 (0.227) | 1.124 (0.234) | 1.348 (0.192) | 1.267 (0.168) | 1.442 (0.225) | 1.239 (0.159) |
| CBF:CI | 0.64 (0.06) | 0.64 (0.06) | 0.62 (0.06) | 0.61 (0.07) | 0.53 (0.05) | 0.47 (0.06) | 0.43 (0.07) | 0.55 (0.07) |

TABLE II. *Effects on regional cardiac function of increasing concentrations of isoflurane with a low dose of verapamil before and after application of critical constriction to the LAD coronary artery (mean* (SEM)). *EDL = End-diastolic length; %SS = % systolic shortening, %PSS = % post-systolic shortening.* **$P < 0.05$ (analysis of variance followed by Duncan's multiple range test)*

| | Before critical constriction | | | | After critical constriction | | | |
|---|---|---|---|---|---|---|---|---|
| Isoflurane MAC: | 0.75 | 1 | 1.5 | 0.75R† | 0.75 | 1 | 1.5 | 0.75R† |
| Apical segment | | | | | | | | |
| EDL (mm) | 13.62 (0.59) | 13.66 (0.60) | 13.84 (0.64)* | 13.72 (0.60) | 13.99 (1.06) | 14.16 (1.10) | 14.53 (1.26)* | 14.32 (1.14) |
| %SS | 10.88 (1.96) | 8.52 (1.87)* | 5.73 (1.74)* | 9.57 (2.55) | 13.38 (2.71) | 10.98 (2.66) | 5.70 (2.27)* | 13.07 (2.90) |
| %PSS | 25.3 (8.3) | 30.1 (10.9) | 47.1 (11.8)* | 36.3 (14.7)* | 10.4 (7.7) | 13.2 (6.2) | 49.9 (9.4)* | 20.3 (4.5) |
| Basal segment | | | | | | | | |
| EDL (mm) | 13.64 (0.80) | 13.63 (0.77) | 13.89 (0.79)* | 13.61 (0.79) | 12.97 (1.38) | 13.02 (1.39) | 13.42 (1.44)* | 13.15 (1.44) |
| %SS | 12.26 (2.71) | 7.94 (1.15)* | 6.09 (1.11)* | 10.24 (1.22) | 9.19 (1.35) | 6.52 (1.12) | 4.61 (1.33)* | 8.03 (1.57) |
| %PSS | 16.1 (4.81) | 23.8 (7.53)* | 25.9 (6.45)* | 16.8 (5.06) | 23.4 (9.90) | 27.6 (7.90) | 27.9 (9.10) | 27.6 (9.00) |

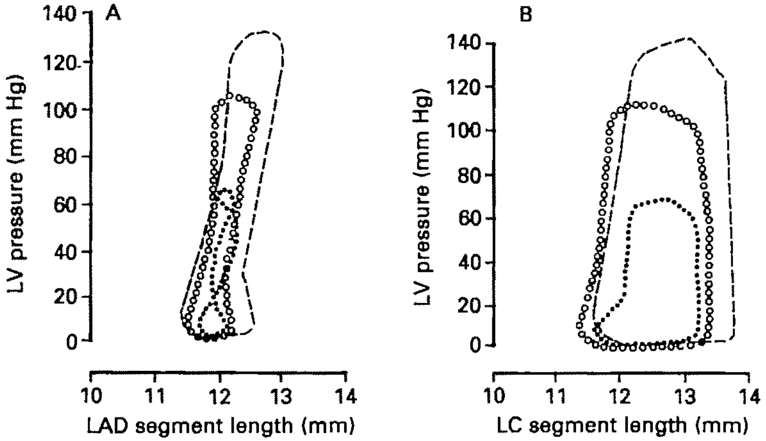

FIG. 2. Pressure–length loops at 0.75 (broken lines), 1.0 (open circles), and 1.5 MAC isoflurane (closed circles) for: A, the apical segment (LAD); B, the basal segment (LC). Profound dysfunction developed in the apical segment at 1.5 MAC isoflurane.

isoflurane. Critical coronary constriction caused significant reductions in CBF: 23% at 0.7 MAC isoflurane, 27% at 1.0 MAC and 31% at 1.5 MAC. The increased concentrations of isoflurane produced the same dose-related effects on systemic haemodynamic values before and after critical constriction and there was no statistical difference between values before and after critical constriction (table I). The reductions in CBF were similar to those in CPP and, at any perfusion pressure, CBF was smaller after critical coronary constriction (fig. 1).

In the LAD territory, EDL increased significantly on increasing the isoflurane concentration, and SS decreased to the same extent before and after critical constriction. PSS increased to a maximal value of 50% of the systolic shortening. Critical constriction of LAD did not modify the effect of deepening isoflurane anaesthesia on the pressure–length loops (fig. 3).

In the LC territory, EDL increased significantly but the dilatation was less pronounced than in the pre-critical constriction period. SS decreased to values slightly less than in the pre-critical constriction period, but the differences did not reach statistical significance. PSS was not modified significantly (table II).

## DISCUSSION

The main findings of the present study may be summarized as follows:

(1) In the presence of verapamil, increases in isoflurane concentrations caused dose-dependent myocardial depression.

(2) The association of verapamil with isoflurane caused myocardial dysfunction that worsened at high isoflurane concentrations.

(3) The vasodilatation generally associated with high concentrations of isoflurane, in both the systemic and the coronary circulations, did not occur in the presence of verapamil.

(4) The effects of isoflurane were not modified by application of a critical coronary constriction.

Because calcium antagonists are used extensively in patients with ischaemic heart disease or hypertension, we have examined the effect of isoflurane in the presence of a constant infusion of verapamil in both normal and compromised myocardium, using a model of critical LAD coronary stenosis [13–15]. In order to approach clinical conditions of a long-term treatment, verapamil was administered to achieve small plasma concentrations (between 45 and 49 ng ml$^{-1}$) and the effects of isoflurane were tested at three concentrations relevant to clinical anaesthesia. Moreover, the acute preparation used in this study mimics the clinical situation in which patients undergo surgery under anaesthesia.

When used separately, isoflurane and verapamil are both potent vasodilators [16–18]. This action facilitates left ventricular ejection and allows cardiac output to be maintained despite the negative inotropic effects of the drugs.

Not surprisingly, association of isoflurane and verapamil shows an additive depression of con-

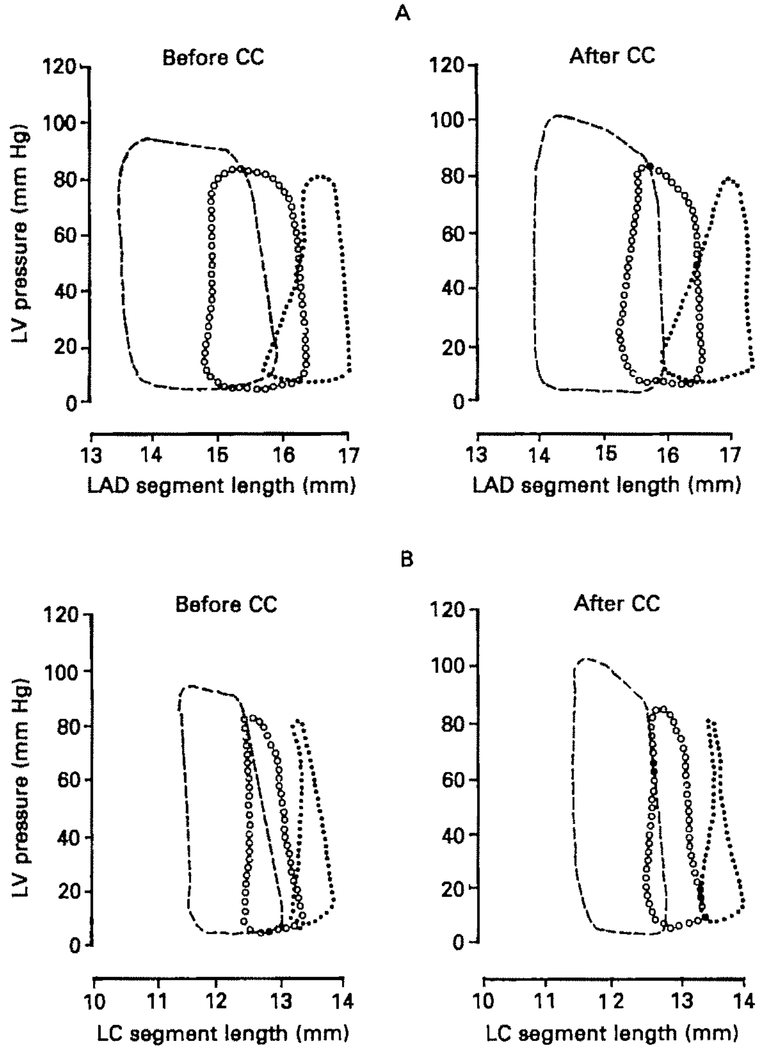

FIG. 3. Pressure–length loops at 0.75 (broken lines), 1.0 (open circles), and 1.5 MAC isoflurane (closed circles) for: A, the apical segment (LAD); B, the basal segment (LC)—before and after critical coronary artery constriction (CC), showing that the changes in regional function were little modified by critical coronary constriction.

tractility and pump function and a negative dromotropic action, as demonstrated by several studies in dogs [1, 3, 6]. Our study shows that isoflurane induced dose-related depression in both contractility (LVd$P$/d$t_{max}$) and pump function (left ventricular peak power, stroke volume, stroke work and systolic shortening) when associated with a constant, small plasma concentration of verapamil. These effects were reversible and may be attributed to isoflurane, as decreasing the isoflurane concentration allowed haemodynamic values to return to baseline. These results are consistent with those of other studies, although experimental and drug administration procedures differed slightly. Campos and Kapur [4], in an acute model using similar inspired isoflurane concentrations and larger doses of verapamil, observed greater systemic pressure, contractility and filling pressure, associated with less systemic vascular resistance at 1 MAC isoflurane than in our study. Kapur and colleagues [3], in a chronically instrumented model, using 1.34% isoflurane, demonstrated greater global performance (LVd$P$/d$t_{max}$ and mean arterial pressure) than our model at 1 MAC, whereas Rogers and colleagues [6], with plasma concentrations of verapamil 80–95 ng $ml^{-1}$, in a chronic model, showed slightly less deleterious effects of 1.6% isoflurane. Kates and co-workers [1], testing three different concentrations of isoflurane (0.75, 1.05, 1.4%) with verapamil concentrations of 35–70 ng $ml^{-1}$ reported results similar to ours in contractility and pump function, in a model with controlled preload and afterload (haemodiluted right heart bypass preparation). In our study, systemic vascular resistance remained essentially unchanged at a time cardiac output and mean arterial pressure were markedly reduced. This is in agreement with the observations by Kapur and colleagues [3], who demonstrated that vascular resistance was not decreased by the association isoflurane–verapamil, in contrast with observations when isoflurane or verapamil was used alone. However, our results differ from those of Kates and co-workers [1], who showed a reduction in vascular resistance. This discrepancy may be related to decreased blood viscosity, as the study of Kates involved haemodilution which reduced systemic vascular resistance.

In a study using i.v. or intracoronary nifedipine, Serruys and colleagues [19] attributed the smaller myocardial depression after i.v. nifedipine to a reflexly mediated increase in sympathetic activity which compensated for the negative inotropy of nifedipine. In our study, the lack of increase in heart rate in the presence of hypotension may indicate that verapamil–isoflurane, or isoflurane alone, decreased the baroreflex response. Thus isoflurane may have unmasked and potentiated the inotropic depressant effect of verapamil.

The increases in isoflurane concentration caused reductions in CPP by 11% and 32% (1 and 1.5 MAC) and in CBF by 13% and 33.5% (1 and 1.5 MAC) without change in CVR. The reduction in CBF paralleled those in CPP and in the most important determinants of myocardial oxygen demand (contractility and arterial pressure). These results differ substantially from those of studies of isoflurane alone [20] which have shown reductions in CVR of between −15% and −47%, associated with small increases in CBF [20–23]. In the study by Priebe [23], the ratio of coronary to aortic blood flow increased by 16–24%, while it did not increase in our study, reflecting that lack of coronary vasodilatation.

While the effect of the interaction verapamil–isoflurane on systemic haemodynamics has been well documented, little is known about regional function. Using sonomicrometry, Kates and colleagues [1] reported only systolic shortening data. With small concentrations of verapamil, they found decreases in SS ranging from 10 to 26% with increasing isoflurane concentrations. We found a greater decrease (−22 to −47%) in SS over a comparable range of isoflurane concentrations. This difference may have been a result of the way in which length signals were recorded. We used a high paper speed (250 mm $s^{-1}$) and defined end-systole as the cessation of aortic flow; this allowed us to determine true systolic shortening accurately and to differentiate systolic from post-systolic shortening. When length signals are recorded slowly, it may be difficult or even impossible to differentiate between systolic and post-systolic shortening, so that *total* shortening is reported instead of *systolic* shortening. In our study, total shortening (SS plus PSS) decreased by 14–27%, almost exactly as in the study reported by Kates' group [1]. In addition to the reduction in SS, we have observed a dose-dependent exaggeration of regional dysfunction (PSS) mainly in the LAD territory. We have demonstrated in a previous study the occurrence of regional dysfunction when verapamil was added to isoflurane. This dysfunction appeared at a time when CBF was not altered and was attributed to a delay in onset of lengthening because of pharmacological interaction between isoflurane and verapamil on myocardial calcium fluxes [8], as isoflurane exerts a marked effect on the slow calcium channels [24, 25]. In the present study, PSS increased as both CPP pressure and CBF decreased, suggesting that inadequate subendocardial perfusion may have developed. Figure 2 shows pressure–length loops obtained in one dog with increasing isoflurane concentrations: PSS and systolic bulging are pronounced at 0.75 and 1.00 MAC isoflurane; the loop obtained at 1.5 MAC isoflurane is similar to the loops described by Lew and colleagues [26] after 3 min of LAD coronary artery occlusion. Thus, if a pharamacological interaction between isoflurane and verapamil can explain regional dysfunction at the smaller concentrations of isoflurane, subendocardial ischaemia is more likely to be responsible for the dysfunction observed with 1.5 MAC isoflurane.

Impaired relaxation and increased end-diastolic stiffness are usual features of myocardial ischaemia [27]. Impaired relaxation was indicated,

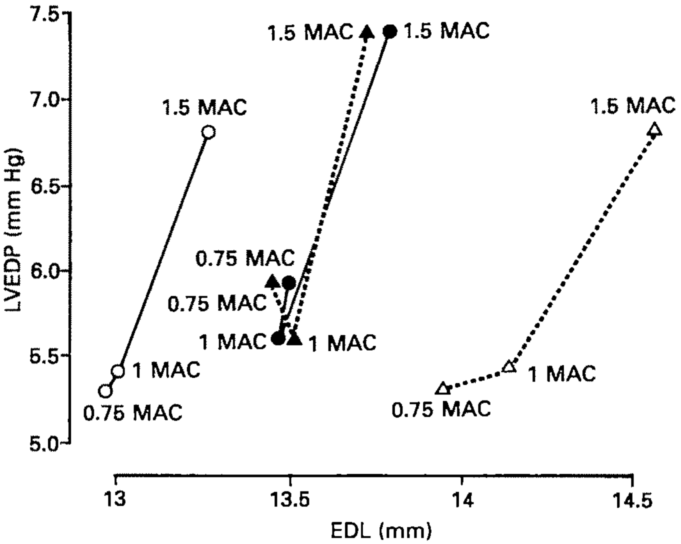

FIG. 4. Relationship between left ventricular end-diastolic pressure (LVEDP) and end-diastolic length (EDL) for the apical segment (open symbols) and the basal segment (closed symbols), before (circles) and after (squares) critical coronary constriction, showing the large increase in LVEDP at 1.5 MAC isoflurane, and the marked dilatation of the compromised segment after coronary constriction.

in the present study, by a prolonged time constant of relaxation and a decreased negative LV$dP/dt_{max}$. Increased end-diastolic stiffness is demonstrated in figure 4, in which a large increase in LVEDP with 1.5 MAC isoflurane may be seen to be associated with a small increase in EDL before or after critical coronary constriction. Three different mechanisms may be involved in this apparent ischaemia: the decrease in CPP to less than 50 mm Hg; an increase in diastolic wall tension because of increases in both end-diastolic pressure and dimension causing redistribution of CBF away from the subendocardium; and the asynchrony of contraction itself which causes mechanical work to be wasted as 50% of the shortening occurs after aortic valve closure and may impede coronary blood flow during the early phase of the diastole. As, in another study [8], the association isoflurane–verapamil caused post-systolic shortening even in animals in which LAD had not been dissected, it can be argued that impairment of regional function is caused by reductions in CPP and CBF and not by surgically induced coronary damage.

Application of critical constriction to the LAD coronary artery did not modify the global haemodynamic response to isoflurane in comparison with pre-constriction data. Coronary blood flow, already reduced by critical constriction, was reduced further by the increase in isoflurane concentration, the parallel shift of the relationship CBF:CPP being a reflection of the critical stenosis (fig. 1). However, regional function in the LAD supply territory fared no worse after critical constriction than before as the isoflurane concentration was increased despite the substantially smaller CBF. This may seem paradoxical, as the depression of metabolic needs was not greater after critical coronary constriction. However, it is possible that dysfunction before coronary constriction was caused both by drug interaction (isoflurane–verapamil) and by subendocardial ischaemia. Verapamil may have enhanced collateral coronary blood so that, after critical coronary constriction, dysfunction was not exaggerated.

In models of regional ischaemia, a compensatory increase in shortening of the normal myocardium has often been reported [28]. In the case of ischaemic dysfunction induced by isoflurane, such compensatory enhancement has been reported by Priebe [29]. It is attributed usually to an increase in end-diastolic dimensions (Frank–Starling mechanism) and to intraventricular unloading as the ischaemic segment may be distended during early systole, thus increasing the scope for shortening of the normally perfused segment. No such enhancement occurred in this study. After critical constriction, basal end-diastolic length decreased and therefore the Frank–Starling mechanism could only reduce shortening. Moreover, the whole myocardium was subjected to the effects of the association verapamil–isoflurane, even though pathological patterns of dysfunction were prominent only in the apical area of the ventricle. Thus the basal area supplied by the LC coronary artery cannot be considered "normal", as it is subjected to the effects of two drugs with additive negative inotropy.

A steal phenomenon has been documented in the ischaemic myocardium as a result of administration of isoflurane [21, 30]. As isoflurane did not cause systemic or coronary vasodilatation in the presence of verapamil, a steal phenomenon would not be anticipated. Indeed, in this study indirect evidence suggested that, when verapamil was present, a steal phenomenon did not develop, because wall motion did not deteriorate more in the LAD segment after critical constriction and because systolic shortening in LC segment did not improve after critical constriction of LAD, suggesting that redistribution of coronary flow to the basal myocardium did not occur.

## ACKNOWLEDGEMENTS

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# THE AUDITORY STEADY STATE RESPONSE DURING SUFENTANIL ANAESTHESIA

G. PLOURDE AND J. F. BOYLAN

## SUMMARY

*The auditory steady state response (ASSR) is a sinusoidal evoked potential elicited by rapidly repeated auditory stimuli. The ASSR was recorded in eight patients during high-dose sufentanil anaesthesia for cardiac surgery in order to assess its usefulness as a measure of the level of consciousness. The electroencephalogram (EEG) was recorded for comparison. The ASSR was present before induction in all patients. It was attenuated severely or possibly abolished with loss of consciousness, and reappeared at low amplitude 5–10 min later and remained attenuated until the end of surgery. The amplitude increased with early signs of awakening in the Intensive Care Unit. With few exceptions, changes in the simultaneously recorded EEG were similar to those of the ASSR. The ASSR deserves further evaluation as a tool for monitoring level of consciousness during high-dose opioid anaesthesia.*

**KEY WORDS**

*Analgesics: sufentanil. Brain. electroencephalogram, auditory evoked potentials, auditory steady state response Monitoring: electroencephalography, auditory evoked potentials.*

It is difficult to assess the level of consciousness during high-dose opioid anaesthesia. Concomitantly administered neuromuscular blocking agents interfere with ability to move in response to verbal command or pain. Use of beta-blockers and drugs with vasodilating properties may mask autonomic signs of light anaesthesia. Periodic reports of recall of intraoperative events with high-dose opioid anaesthesia [1] have led to the assertion that opioids do not maintain unconsciousness [2], despite their ability to produce sedation and unresponsiveness [3, 4]. Large doses of opioid produce slowing of the electroencephalogram (EEG) with predominance of delta activity [5–9]. These changes, however, do not imply unconsciousness [10, 11]. Similar changes may occur in conscious patients with minimal mental impairment [10]. Satisfactory evaluation of the level of consciousness is, therefore, not yet available.

The auditory steady state response (ASSR) is a sustained sinusoidal evoked potential elicited by repetitive auditory stimuli. It appears when the rate of stimulus delivery is sufficiently fast to produce overlapping of the responses to each stimulus [12–14]. The ASSR is most prominent with stimulus rates around 40 Hz. The ASSR amplitude reflects the level of arousal or alertness; it is reduced by approximately 50% in both physiological and sedative-induced sleep [15, 16]. Spontaneous amplitude fluctuations over approximately 1 min have been reported in normal volunteers and these may reflect concurrent changes of arousal [17]. The ASSR is abolished or attenuated markedly during nitrous oxide–isoflurane anaesthesia [18, 19].

We studied the effects of high-dose sufentanil on the ASSR in eight patients undergoing coronary artery surgery. The EEG was recorded for comparison.

## PATIENTS AND METHODS

After institutional Ethics Committee approval and written informed consent, we studied eight patients (seven males), who were devoid of

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hearing or neurological disorder. All were undergoing elective coronary artery bypass grafting. The mean age was 56 yr (range 41–68 yr).

*Anaesthetic technique*

In addition to their routine nitrate, beta-blocker and calcium channel blocker medication, the patients were premedicated with oral lorazepam 0.04 mg $kg^{-1}$ 90 min before operation. Anaesthesia was induced with sufentanil 5 µg $kg^{-1}$, injected over 3–5 min and preceded by pancuronium 0.02 mg $kg^{-1}$. After the patient failed to open the eyes on two consecutive commands, pancuronium 0.08 mg $kg^{-1}$ was given to facilitate tracheal intubation. The lungs were ventilated mechanically to maintain the end-tidal partial pressure of carbon dioxide at 4 kPa (SARA mass spectrometer, Allegheny International). The pulmonary artery catheter was then inserted. Further increments of sufentanil 1–2 µg $kg^{-1}$ were given before skin incision, sternotomy, aortic cannulation and after cardiopulmonary bypass (CPB) to prevent or correct hypertension and tachycardia. Arterial hypertension (MAP greater than 30% of preoperative values), and tachycardia (greater than 90 beat $min^{-1}$) not corrected by sufentanil, were treated with nitroglycerin or nitroprusside, and propranolol, respectively. Nasopharyngeal temperature was monitored continuously. Non-pulsatile cardiopulmonary bypass was used with a flow of 2.0 litre $m^{-2}$ $min^{-1}$ under moderate hypothermia (28 °C). Bubble oxygenators and arterial filters were used. No carbon dioxide or glucose was added to the perfusion. The arterial partial pressure of carbon dioxide (measured at 37 °C) was 4–5.3 kPa. Full rewarming (urinary bladder temperature greater than 34.5 °C) was achieved before discontinuation of CPB. The patients were questioned about recall of intraoperative events after 2 days, and also at 1–3 months after the operation.

*Auditory steady state responses (ASSR)*

An IBM-AT compatible computer with two analog-to-digital (a–d) conversion cards was used for stimulus control and signal acquisition.

*Stimuli.* Tonebursts (500 Hz, 15 ms duration, 5 ms rise/fall time, 90 dB peak sound pressure level (SPL)) were presented binaurally at a rate of 40 $s^{-1}$ via insert earphones (Etymotic Research, model ER3A). The frequency was increased randomly (on average 10 times per minute) to 900 Hz for 75 ms to produce "target" stimuli, to which patients were required to respond by button press. (This was, of course, possible only when the patients were not paralysed.) The percentage of detected targets (i.e. button press present) was used to measure responsiveness [20].

*Recording.* The EEG was recorded with gold-plated cup electrodes attached with saline gel and collodion. Inter-electrode impedances were less than 5 kΩ (10 Hz). Three electrodes were placed according to the International 10–20 system [21] at frontal (Fz), central (Cz) and parietal (Pz) midsagittal scalp locations, with reference to the right mastoid (M2). A fifth channel was used to record button presses. Vertical eye movements (EOG) were recorded to allow rejection of data contaminated by eye movements. The amplification band-pass was from 0.16 to 100 Hz. The amplifiers (Grass Model P511K) followed the EEG convention that negativity at the scalp electrode, relative to the reference (mastoid), was plotted upwards.

The a–d epoch lasted 1490 ms, with a sampling frequency of 668 Hz per channel and a resolution of 12 bits. The interval between onset of successive epochs was 2000 ms signal. (The 510 ms between the end of an a–d epoch and the beginning of the next epoch was required for averaging and other computations.) Epochs contaminated by ocular movements or other artefacts were rejected. The rejection level was ±87.5 µV on all channels. Successive epochs were averaged on-line in groups of 30–60, corresponding to recording periods of 90 or 180 s. (A 90-s recording consisted of 45 epochs of 2 s. On average, 33% of these 45 epochs included "target" stimuli and could not be used for the ASSR. Thus about 30 epochs were used for ASSR, the exact number depending on the actual number of target stimuli (probability of 0.33 per epoch) and the number of epochs rejected because of artefacts.)

*Measurements.* Responses were analysed using fast Fourier transform [22] of the unfiltered averaged traces.

*Electroencephalogram*

*Recording.* The EEG was recorded for 2 s after each ASSR average waveform. The recording parameters were identical to those used for the ASSR.

*Measurements.* The following measures were derived from the power spectrum of the EEG: median [23] and spectral edge (95 % quantile) [24] frequencies, and relative power in the delta (0.5–3.4 Hz) frequency band. These measurements were determined after digitally filtering the EEG from 0.5 to 32 Hz, in accordance with current anaesthetic practice [25].

### *Design*

Recordings were obtained at the following times: *pre-induction* (15–45 min before induction of anaesthesia); *early induction* (from the beginning of the sufentanil injection to loss of consciousness, judged by failure to open the eyes on command); *late induction* (the 90-s period immediately after loss of consciousness); *post-intubation* (tracheal intubation was performed 4–5 min after the beginning of induction. Recording was started 1 min after intubation and lasted 15–25 min. The pulmonary artery and urinary bladder catheters were inserted during this period); *pre-CPB* surgery (before, during or after aortic and atrial cannulation, the only time when electrocautery was not used); *CPB* (hypothermia) (28 °C); *CPB* (normothermia) (before discontinuation of CPB); *post-CPB* (from 5 to 20 min after haemodynamic stability); *ICU* (90–120 min after arrival in the Intensive Care Unit).

Before each recording (30–60 epochs), a message informed the patient, addressed by his/her first name, that all was well and instructed him/her to count the target stimuli mentally, if possible. This message was through the insert earphones. During pre-induction, early induction and ICU the patient was asked also to keep the eyes closed and to respond to each auditory target stimulus by a button-press. Within each period (other than induction), multiple ASSR average waveforms were obtained. They were averaged digitally before measurement.

Because of time constraints during induction, the EEG was recorded only during late induction. No EEG data are available, therefore, for early induction.

### *Statistical analysis*

The Rayleigh test for phase coherence [26, 27] was used to determine if the responses could be distinguished reliably from background noise. The differences between recording periods were analysed by one-way analysis of variance (ANOVA) tor repeated measures, using the Geisser–Greenhouse adjustment of the significance levels [28, 29]. Tukey's HSD [28] test was used for *post-hoc* comparisons. Criteria for significance were $P < 0.05$ for ANOVA and $P < 0.01$ for the comparisons to reduce the likelihood of spurious significance.

## RESULTS

### *Anaesthesia*

The mean doses of sufentanil for all patients were 5.7 $\mu g\ kg^{-1}$ at induction, 1.3 $\mu g\ kg^{-1}$ before skin incision and 1.8 $\mu g\ kg^{-1}$ before sternotomy. Four patients received additional sufentanil (mean dose for the four patients = 2.6 $\mu g\ kg^{-1}$) after sternotomy or during aortic dissection to treat arterial hypertension (three patients) or tachycardia (one patient). These four patients later required intraoperative vasodilator therapy or propranolol, or both. Two required enflurane briefly to produce rapid control of severe hypertension, one during aortic cannulation and the other after emergence from CPB. (The recordings obtained during administration of enflurane were not included in the analysis. Recording was resumed only when the enflurane could no longer be detected in expired gas.) Three patients received sufentanil (mean dose 1.2 $\mu g\ kg^{-1}$) after CPB. The mean duration of surgery was 228 (SD 59) min and average duration was 99 (58) min. Three patients required adrenaline or noradrenaline during termination of CPB. Inotropes were discontinued within 12 h. All patients had an uneventful recovery and tracheal extubation took place on the first morning after operation. All patients denied conscious recall of intraoperative events.

Mean (SD) nasopharyngeal temperature was 35.9 (0.4) °C during post-intubation, 35.4 (0.5) °C during pre-CPB, 29.1 (2.4) °C during CPB (hypothermia), 35.1 (1.4) °C during CPB (normothermia), 35.6 (1.0) °C during post-CPB and 36.6 (0.8) °C in the ICU.

### *Target stimuli detection and level of sedation*

The detection rate was 66 (SD 26) % during pre-induction. There was a significant ($P < 0.01$, Tukey's HSD) reduction in detection rate during early induction (12 (11) %) and ICU (11 (13) %). The number of patients who detected 5 % or more target stimuli was eight during pre-induction, five during early induction and four during ICU (fig. 1). For these three periods, the percentage of

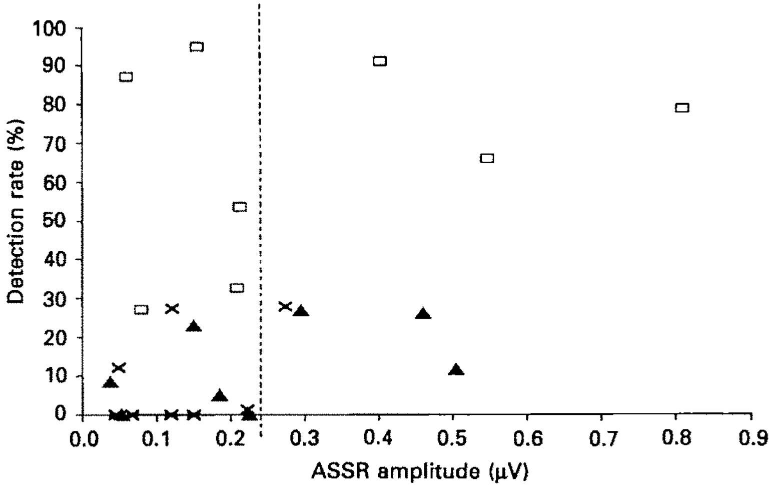

FIG. 1. Detection of target stimuli as a function of the amplitude of the ASSR during pre-induction (□), early induction (▲) and ICU (×) periods No target stimuli were detected during late induction. The detection rate during ICU may have been underestimated because of difficulty in holding the button-press switch. Neuromuscular blocking agents precluded measurement of responsiveness during the other periods. The detection rate for points to the right of the dotted line exceeds 5%.

detected target always exceeded 5% when the ASSR amplitude was 0.22 μV or more. With ASSR amplitudes less than 0.22 μV, the detection rate ranged from 0 to 95%. During the other periods, anaesthesia and muscle paralysis prevented button-pressing.

During the pre-induction period, the patients were either drowsy or intermittently asleep and the eyes were closed most of the time. All opened their eyes on request, usually on the first instance. During sleep, however, the request had to be repeated once or twice to arouse the patient. Some patients fell asleep towards the end of individual 180-s recording periods.

It was extremely difficult to assess the level of consciousness in the ICU. Five patients opened their eyes at least once. There were minute-to-minute changes in ability to detect target stimuli and open the eyes on command. The relationships between these two measures could not be assessed because the changes were too rapid.

TABLE I. *Auditory steady state responses (mean (SD)). §Based on only five patients and not included in the ANOVA. **Phase coherence present (i.e. response significantly different from residual noise) (P < 0.01). †† Significantly less than pre-induction (P < 0.01) (Tukey's HSD)*

| Period | Amplitude (μV) |
|---|---|
| Pre-induction | 0.30 (0.27)** |
| Early induction | 0.24 (0.18)** |
| Late induction | 0.05 (0.05)†† |
| Post-intubation | 0.12 (0.10)** |
| Pre-CPB | 0.09 (0.10)**†† |
| CPB (hypothermia)§ | 0.05 (0.03) |
| CPB (normothermia) | 0.08 (0.05)†† |
| Post-CPB | 0.09 (0.05)†† |
| ICU | 0.14 (0.09)** |
| ANOVA | $P < 0.05$ |

*ASSR and EEG*

Recordings during CPB (hypothermia) are available for only five patients because of ambiguity in the recording instructions. These results could not therefore be included in the analysis of variance, but they will be described in the tables and figures.

The ASSR was clearly visible on the amplitude spectra relative to adjacent frequencies in all patients during pre-induction. However, it was small (0.06 and 0.08 μV) in two patients. Significant ($P < 0.01$) decreases in ASSR amplitude occurred during late induction, pre-CPB, CPB (normothermia) and post-CPB (table I). During late induction, a small 40-Hz peak could still be identified relative to adjacent frequencies in three patients. The ASSR was significantly different ($P < 0.01$, phase coherence across patients) from background noise during all periods, except late induction, CPB (hypothermia), CPB (normo-

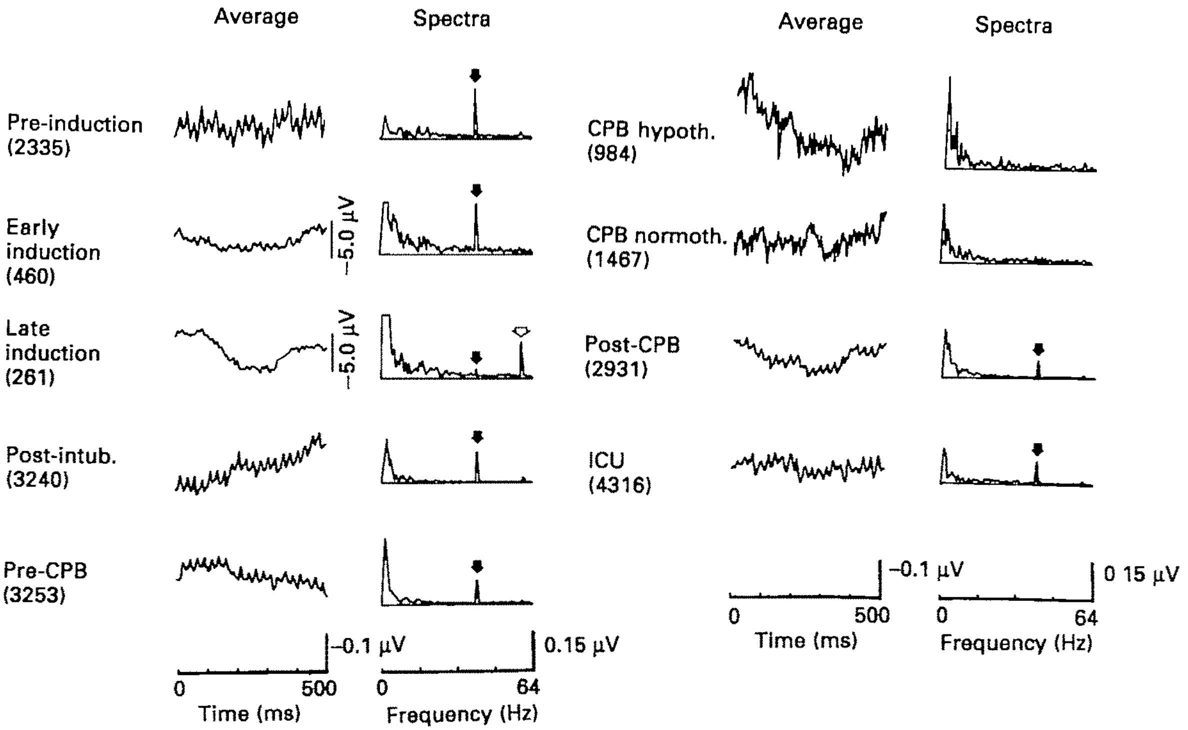

FIG. 2. For each period, the first 500 ms of the grand-average waveform (all patients included) is depicted, with the corresponding amplitude spectrum obtained from the fast Fourier transform of the entire average waveform. The number of epochs included in the average waveform is indicated in parentheses The ASSR peaks (i.e. the amplitude at 40 Hz) are indicated by the solid arrows. No ASSR peak could be identified during CPB. The large peak during late induction (open arrow) is 60-Hz noise (power line). CPB = Cardiopulmonary bypass.

thermia) and post-CPB. (During post-CPB the significance level was $P < 0.025$.)

Figure 2 shows the average waveforms for all patients and the corresponding amplitude spectra. Figure 3 shows the waveforms of one patient.

EEG results are presented in table II. Compared with pre-induction, the median frequency was reduced significantly during all periods. The spectral edge frequency was reduced significantly during all periods except ICU. The relative delta power was increased significantly in all periods.

## DISCUSSION

The reduction in the ASSR during sufentanil anaesthesia was equal to or greater than that seen during stage III or IV sleep [15, 16]. Pre-induction amplitude was reduced by about 25% compared with unmedicated subjects [19], probably reflecting the sedation caused by premedication [16].

The ASSR was attenuated markedly or abolished during late induction (when responsiveness was lost) and during CPB. The very small 40-Hz peak during late induction (fig. 1) was indistinguishable from background noise (test of phase coherence across subjects). More observations are needed to determine if the ASSR is abolished or only attenuated profoundly. Nevertheless, severe attenuation of the ASSR during late induction probably indicates profound impairment of the level of arousal [19] caused by maximal plasma and brain concentrations of sufentanil [30].

The increased level of 60-Hz noise (fig. 2, open arrow) during late induction does not account for the reduction of the ASSR peak; it resulted from touching the patient for mask ventilation. This causes a transfer of energy from power lines by stray inductance [31]. Because the phase of the ASSR is locked to the stimuli, while that of the noise is not [31], contamination by 60-Hz noise

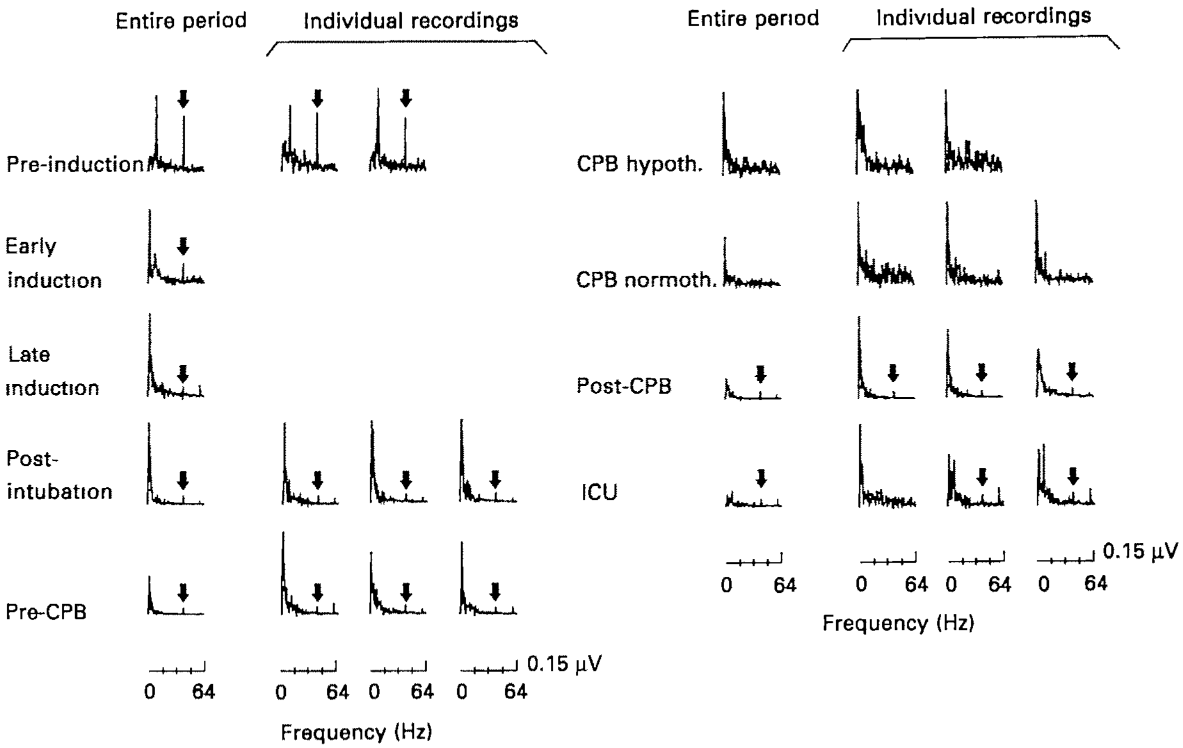

FIG. 3. Waveforms from one patient. For each period, the amplitude spectrum of the average waveform for the entire period is on the left; spectra of individual recordings are on the right. The duration of the individual recordings was 180 s, except during early induction (recording stopped at 123 s when responsiveness was lost) and late induction (90 s). The numbers of individual recordings included in the average waveform for the entire period were: 2 for pre-induction, 1 for early and late induction, 3 for post-intubation, 8 for pre-CPB, 2 for CPB-hypothermia, 5 for CPB-normothermia, 8 for post-CPB and 12 for ICU. Phase coherence was present within the following periods: pre-CPB, post-CPB and ICU. Phase coherence was not assessed within the other periods because of the small number of recordings. To reduce the space required, a maximum of three individual recordings are shown. For periods including more than three recordings, the individual recordings shown were selected from 1st, 2nd and last third of the period. Arrows point to the 40-Hz peaks. Note the general similarity between average (on the left) and individual (on the right) recordings. The percentage of detected target stimuli was 79 during pre-induction, 28 during early induction and 27 in the ICU.

TABLE II *Electroencephalogram (mean (SD)). §Because of time constraints, the EEG was not recorded during early induction. ‡Based on only five patients and not included in the ANOVA. **Significantly less than pre-induction* (P < *0.01*)

| Period | Median frequency (Hz) | Spectral edge frequency (Hz) | Relative delta (0.5–3.4 Hz) power |
|---|---|---|---|
| Pre-induction | 6.3 (3.8) | 23.5 (2.0) | 0.44 (0.19) |
| Late-induction§ | 1.1 (0.4)** | 3.9 (1.3)** | 0.94 (0.20)** |
| Post-intubation | 1.3 (0.3)** | 7.1 (2.7)** | 0.88 (0.05)** |
| Pre-CPB | 1.5 (0.8)** | 8.1 (3.9)** | 0.87 (0.08)** |
| CPB (hypothermia)‡ | 2.3 (1.3) | 12.6 (7.8) | 0.70 (0.16) |
| CPB (normothermia) | 1.4 (0.3)** | 9.4 (4.5)** | 0.83 (0.06)** |
| Post-CPB | 1.5 (0.4)** | 8.7 (2.7)** | 0.82 (0.08)** |
| ICU | 2.9 (1.8)** | 17.8 (8.7) | 0.67 (0.17)** |
| ANOVA | $P < 0.01$ | $P < 0.001$ | $P < 0.001$ |

would not affect the ASSR unless it caused saturation of the amplifiers, which it did not. (The phase of the ASSR indicates the relative timing between the response and the stimuli. It is the steady-state equivalent of latency [31].)

The ASSR reappeared clearly during the post-intubation period and the amplitude was close to that in the ICU and similar to that seen immediately upon emergence from isoflurane anaesthesia [19]. This probably reflects lightening of anaesthesia, attributable to the rapid decrease in plasma and brain concentrations of sufentanil [30]. It might therefore be prudent routinely to administer additional sufentanil (or other anaesthetic) after tracheal intubation. Preservation of the ASSR does not definitely indicate awareness or consciousness, however. The ASSR may be recorded in comatose patients, particularly with less severe grade 1 and 2 coma [32]. Preservation of the ASSR, despite the amplitude reduction, indicates that synchronization is maintained in the neuronal circuits generating the ASSR, probably from the reticular formation (which controls arousal and sleep–wake cycles [33]), the medial geniculate and the auditory cortex [13].

The ASSR was absent during CPB with hypothermia or normothermia. In common with the 60-Hz contamination from power lines, cyclical artefacts from the roller-pumps cannot account for disappearance of the ASSR and increased residual noise does not provide a satisfactory explanation as it could mask only a very small response. The absence of the ASSR is probably attributable to depression of the brain by hypothermia or by physiological disturbances associated with rewarming [34].

The mean ASSR amplitude in the ICU was larger than in any other period except pre-induction and early induction. Detailed analysis of any relationship between the ASSR and the level of consciousness in the ICU could not be performed. The level of consciousness was difficult to assess and seemed to change rapidly. However, the following observations are offered. In general, consciousness in the ICU was impaired more than that during pre-induction (in contrast to pre-induction, the patients were often not rousable), although the patients did not have adequate surgical anaesthesia. Their level of consciousness was therefore between that of sedation and that of surgical anaesthesia. The ASSR amplitude in the ICU was also between that of pre-induction and that of surgical anaesthesia.

The attenuation of the ASSR by sufentanil contrasts with the absence of an effect of high-dose fentanyl on the transient middle latency response (MLR) [35]. The ASSR results from the superimposition of individual MLR. The amplitude of the ASSR can be predicted when the MLR is known, if one assumes that the neural generators behave linearly [31]. It would be interesting to compare the ASSR with the MLR during sufentanil anaesthesia. If sufentanil alters the MLR, the changes could perhaps explain the attenuation of the ASSR. If, on the other hand, the MLR is not modified by sufentanil, one would have to invoke non-linearities of the neural generators to account for the ASSR attenuation [31].

The ASSR may possibly be useful to predict responsiveness during paralysis with neuromuscular blockers. Responsiveness, defined as the ability of any one patient to detect at least 5% of target stimuli within a single period (pre-induction, early induction and ICU), was always present when the ASSR amplitude exceeded 0.22 μV (fig. 1). An ASSR amplitude less than 0.22 μV, however, did not imply unresponsiveness. This confirms that arousal (measured by the ASSR) and responsiveness can be dissociated [36]: neuro-vegetative patients may be unresponsive despite near normal arousal [36], and simple signal detection tasks can be performed during Stage II sleep, a state of low arousal [37]. The ability of the EEG to predict responsiveness to target stimuli could not be evaluated because we did not record the EEG during early induction. The EEG is probably not better than the ASSR, however, as the pronounced slowing of the EEG by opioids precedes loss of consciousness [38]. The relationship between the ASSR and responsiveness appears to be as follows: loss or very severe attenuation of the ASSR probably implies unresponsiveness (e.g. late induction); an ASSR greater than 0.22 μV probably implies responsiveness; intermediate ASSR amplitudes allow no prediction.

In general, the changes in EEG paralleled those of the ASSR. However, there persisted a significant difference between pre-induction and recovery for the median EEG frequency and the relative delta power. This difference was not significant for the ASSR or for the EEG spectral edge frequency. Nevertheless, the ASSR may have provided more information than the EEG. Its marked attenuation during late induction and its disappearance during CPB are probably a more reliable indicator of unconsciousness than is the EEG. Widespread delta activity (in contrast to burst-suppression or isoelectricity) is not always associated with unconsciousness [10]. Another advantage of the ASSR is that the ASSR is influenced less by muscle artefacts than are univariate EEG descriptors [19]. Fortunately, there is no need to choose between the ASSR and the EEG. The recording procedure could be modified to record and display the ASSR and the EEG concurrently.

## ACKNOWLEDGEMENTS

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# POSSIBLE INVOLVEMENT OF INOSITOL–LIPID METABOLISM IN MALIGNANT HYPERTHERMIA†

J. SCHOLZ, N. ROEWER, U. RUM, W. SCHMITZ, H. SCHOLZ AND J. SCHULTE AM ESCH

## SUMMARY

*$\alpha$-Adrenoceptor stimulation may induce malignant hyperthermia (MH)* in vivo. *Consequently, we have investigated the effects of the $\alpha$-adrenoceptor agonist phenylephrine and, for comparison, the effects of the $\beta$-adrenoceptor agonist isoproterenol on inositol–lipid metabolism of malignant hyperthermia susceptible (MHS) and healthy control (MHN) swine. The experiments were performed on electrically stimulated (frequency 0.2 Hz) trabeculae isolated from the right ventricles of the hearts of MHS and MHN animals. After labelling with [$^3$H] inositol for 6 h, different inositol phosphates were measured by high pressure liquid chromatography, including inositol 1-phosphate, inositol 1,4-bisphosphate, inositol 1,3,4-trisphosphate, inositol 1,4,5-trisphosphate (1,4,5-IP$_3$) and inositol 1,3,4,5-tetrakisphosphate. After stimulation with isoproterenol, the inositol phosphate content did not increase or vary between muscle from MHS and MHN animals. In contrast, all inositol phosphates increased after stimulation with phenylephrine in both muscle types, the effects being greater in MHS than in MHN, especially as regards 1,4,5-IP$_3$ content. As 1,4,5-IP$_3$, a presumed second messenger, has been shown to mobilize intracellular calcium, it is concluded that an enhanced $\alpha$-adrenergic response is involved in the development of MH.*

**KEY WORDS**

*Hyperthermia: malignant Metabolism: inositol phosphates, catecholamines*

Malignant hyperthermia (MH) is a potentially lethal disorder occurring in man, swine and other species [1–3]. Stimulation of $\alpha$-adrenoceptors with phenylephrine has been shown to induce MH in swine [4], whereas $\alpha$-adrenoceptor antagonists are thought to prevent muscle rigors and vasoconstriction [5]. Several studies suggest that the sarcoplasmic reticulum, which controls intracellular calcium fluxes, is involved in MH [6, 7].

Recently, evidence has been accumulating that the presumed second messenger, inositol 1,4,5-trisphosphate (1,4,5-IP$_3$) is involved in $\alpha$-adrenoceptor-mediated effects. Stimulation of $\alpha_1$-adrenoceptors activates a phospholipase C which hydrolyses phosphatidylinositol 4,5-bisphosphate, generating the two presumed second messengers diacylglycerol and 1,4,5-IP$_3$ [8, 9]. 1,4,5-IP$_3$ has been shown to release calcium from intracellular stores in pancreatic cells, hepatocytes and a variety of other cell systems including smooth muscle [8, 10, 11]. Although the calcium releasing function of 1,4,5-IP$_3$ in cardiac and skeletal muscles is still a matter of debate [12–18], it is well established that the $\alpha_1$-adrenoceptor-mediated positive inotropic effect is accompanied by an increase in inositol trisphosphate concentration in rat and man [19–22]. In addition, the phosphorylation product of 1,4,5-IP$_3$, inositol 1,3,4,5-tetrakisphosphate, has been claimed also to possess second messenger function, namely to enhance calcium entry from the extracellular space into the cell [23, 24].

During MH crisis, myocardial disturbances, for example tachycardia, arrhythmia and increased myocardial oxygen consumption, often

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*precede* the increase in body temperature and muscle rigors; thus MH can be a disease of skeletal and cardiac muscle [25]. This hypothesis is either supported [26–30] or rejected [31, 32] by several investigations. The aim of the present work was to determine if the $\alpha_1$-adrenoceptor-mediated positive inotropic effect in cardiac muscle of MH susceptible (MHS) and healthy control (MHN) swine is associated with an increase in cellular 1,4,5-IP$_3$. Other inositol–lipid products were determined also, in order to obtain a more complete view of cardiac inositol–lipid metabolism. For comparison, the effects of the β-adrenoceptor agonist isoproterenol were studied under the same conditions.

## MATERIALS AND METHODS

The study was reviewed and approved by the institutional animal care and use committee. MH susceptible (MHS) Pietrain and healthy control (MHN) swine were studied. They were tested by halothane challenge for MH susceptibility 4 weeks before the investigation, as described previously [33]. The anaesthetized animals (metomidate hydrochloride 10 mg kg$^{-1}$ i.p.; Janssen, Neuss, Germany) were killed by a blow on the head and by bleeding from the carotid arteries. The hearts were excised quickly and suspended in cold (4 °C), aerated bathing solution (composition described below) and delivered to the laboratory within 10 min.

Thin right ventricular trabeculae (diameter < 1 mm, length 6–10 mm) were excised from the hearts of MHS and MHN swine. The preparations were stimulated electrically at a frequency of 0.2 Hz and labelled for 6 h with myo-2-[$^3$H]-inositol 40 µCi ml$^{-1}$ (Amersham, Braunschweig, Germany) in bathing solution. The viability and responsiveness of the heart muscles has been demonstrated previously [20–22, 30, 33, 34]. The bathing solution was a modified Tyrode solution containing (mmol litre$^{-1}$): NaCl 119.8, KCl 5.4, CaCl$_2$ 1.8, MgCl$_2$ 1.05, NaH$_2$PO$_4$ 0.42, NaHCO$_3$ 22.6, Na$_2$EDTA 0.05, ascorbic acid 0.28, and glucose 5.0. It was gassed continuously with 95 % oxygen and 5 % carbon dioxide and maintained at 35 °C with a pH of 7.4 (for details see [22]). All experiments were performed in the presence of the β-adrenoceptor blocking agent (±)-propranolol-HCl 1 µmol litre$^{-1}$ (30 min preincubation) (Rheinpharma, Heidelberg, Germany) to establish identical conditions for all drugs and to avoid any interference from endogenous catecholamines. Muscles, except control muscles, were then incubated for 10 min with either (−)-phenylephrine-HCl (Boehringer, Ingelheim, Germany) 10 µmol litre$^{-1}$ (at which concentration phenylephrine produced a 50 % maximal increase in force of contraction [21]), or (±)-isoproterenol-HCl (Boehringer, Ingelheim, Germany) 10 µmol litre$^{-1}$ (at which concentration it has been shown to produce an equieffective increase in force of contraction in comparison with phenylephrine 10 µmol litre$^{-1}$ [21]). Thereafter, muscles were frozen, homogenized and CHCl$_3$/CH$_3$OH/HCl was added. After centrifugation, samples were freeze-dried, dissolved in water and analysed by high pressure liquid chromatography (Merck-Hitachi, Darmstadt, Germany) on a Partisil 10 SAX column using an ammonium formate gradient (buffered with orthophosphoric acid to pH 3.7) as reported previously [34]. The fractions were counted for radioactivity. The identities of inositol phosphates were secured by comparison with [$^3$H] standards (New England Nuclear, Boston, Massachusetts). Products measured were inositol 1-phosphate (1-IP$_1$), inositol 1,4-bisphosphate (1,4-IP$_2$), inositol 1,4,5-trisphosphate (1,4,5-IP$_3$) and inositol 1,3,4,5-tetrakisphosphate (1,3,4,5-IP$_4$). The compounds were dissolved freshly in bathing solution and this did not change the pH. All others chemicals were of the best grade commercially available. Deionized and double-distilled water was used throughout.

The β-adrenoceptor agonist isoproterenol (10 µmol litre$^{-1}$), which is known to exert its effects via the second messenger cAMP, was studied for comparison. Isoproterenol was also investigated in the presence of propranolol 1 µmol litre$^{-1}$ in order to establish identical conditions. That concentration of isoproterenol was chosen because it has been shown to produce an equieffective increase in force of contraction in comparison with phenylephrine 10 µmol litre$^{-1}$ [21].

Values presented are means (SD). Statistical significance was estimated using Student's *t* test for unpaired observations. $P < 0.05$ was considered significant.

## RESULTS

Figure 1 shows that 1,4,5-IP$_3$, 1,3,4-IP$_3$ and 1,3,4,5-IP$_4$ were detectable in the swine heart, suggesting that the inositol tris-/tetrakisphos-

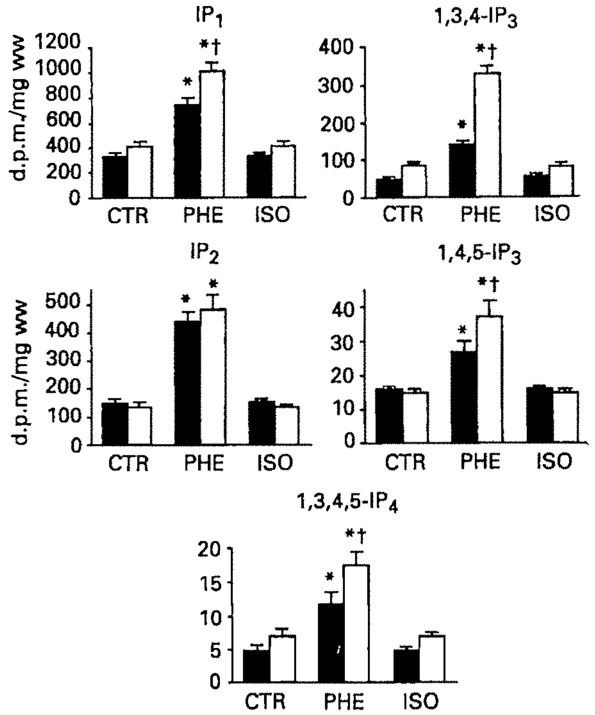

FIG. 1. Effect of phenylephrine (PHE) 10 $\mu$mol litre$^{-1}$ and isoproterenol (ISO) 10 $\mu$mol litre$^{-1}$ on inositol phosphates of malignant hyperthermia susceptible (□) and healthy (■) (MHN) swine. Right ventricular trabeculae were stimulated electrically at a frequency of 0.2 Hz in the presence of propranolol 1 $\mu$mol litre$^{-1}$. Time of incubation was 10 min for PHE or ISO, applied 30 min after addition of propranolol. The data shown are disintegrations per minute (d.p.m.) per mg of tissue, wet weight (ww) (SD). All products were measured in each muscle. The products determined were inositol mono-, bis-, tris- and tetrakisphosphates ($IP_1$, $IP_2$, $IP_3$ and $IP_4$), with assignment of phosphate locants where appropriate. $n = 42$ (7 in each column). Significant differences: *compared with control (CTR); †between respective MHN and MHS values.

phate pathway exists also in the heart of swine. The figure summarizes the effects of the $\alpha_1$-adrenoceptor agonist phenylephrine 10 $\mu$mol litre$^{-1}$ on inositol-lipid metabolism. In these experiments, phenylephrine 10 $\mu$mol litre$^{-1}$ was chosen because at this concentration phenylephrine produced a 50% maximal increase in force of contraction [21]. All inositol phosphate products measured increased after stimulation with phenylephrine in muscle from MHS and MHN animals, compared with control. $IP_1$, $IP_2$, 1,3,4-$IP_3$, 1,4,5-$IP_3$ and $IP_4$ increased to 168–300% of control in MHN and to 246–393% of control in MHS muscle. The inositol phosphates increased more in MHS than in MHN. The effects were significantly greater for $IP_1$, both $IP_3$-isomers and for $IP_4$. There was no difference between control values of MHN and MHS samples.

All inositol phosphate products remained unchanged after stimulation with the $\beta$-adrenoceptor agonist isoproterenol.

## DISCUSSION

The present study suggests a greater increase in 1,4,5-$IP_3$ in MHS than MHN muscle after $\alpha$-adrenoceptor stimulation. Thus it is tempting to speculate that inositol–lipid metabolism is at least in part involved in the development of MH.

The function of 1,3,4,5-$IP_4$ in the heart is unknown, but it has been suggested that it, also, has second messenger function. It has been assumed to be responsible for initiating calcium entry from the exterior in sea urchin eggs and this has been assumed to be dependent on the prior or simultaneous 1,4,5-$IP_3$-triggered discharge of intracellular calcium stores [23, 24]. However, some authors failed to detect 1,3,4,5-$IP_4$ in the heart [35], while others have demonstrated the existence of 1,3,4,5-$IP_4$ in rat hearts [19, 34]. Thus the present study on swine supports the existence of the inositol tris-/tetrakisphosphate pathway in the heart.

During the preparation of this manuscript, in another study, an increased 1,4,5-$IP_3$ content was found in *skeletal* muscle of MHS swine in comparison with control, and in the presence of halothane 1,4,5-$IP_3$ increased further [36]. However, the present study shows an increased content of various inositol phosphates in the *heart*. Thus inositol–lipid metabolism may be an important intracellular mechanism for development of MH, although some aspects of this hypothesis are still speculative. In particular, the functional significance of the increase in inositol phosphate content deserves more detailed discussion. As mentioned above, 1,4,5-$IP_3$ and 1,3,4,5-$IP_4$ can cause an increase in cytosolic calcium concentration. From the marked increase of these products observed in this study, one would expect an increase in force of contraction. However, in a previous study [30] the inotropic effects in the hearts of MHN and MHS swine were similar after stimulation with phenylephrine, whereas the $\beta$-adrenoceptor agonist isoproterenol caused a significantly greater increase in force of contraction. Thus the exact functional importance of 1,4,5-$IP_3$ and 1,3,4,5-

$IP_4$ and their enhanced cardiac increase after α-adrenoceptor stimulation in MHS swine remains to be elucidated. Moreover, one should cautiously consider the possibility that the increased content of the inositol–lipid products may be caused by differential changes in calcium metabolism in MHN and MHS swine, rather than induce these changes; for example, increased intracellular free calcium concentration may facilitate greater activation of calcium-dependent phospholipase C. However, the demonstration of the inositol–lipid metabolism and its enhanced response to halothane and phenylephrine has now been demonstrated in *skeletal* and *heart* muscle of MHS swine, respectively.

In summary, the present study demonstrates that, after α-adrenoceptor stimulation, the inositol phosphate content is greater in the hearts of MHS than MHN swine. Thus it is suggested that the increase in the second messengers, 1,4,5-$IP_3$ and 1,3,4,5-$IP_4$, and their calcium-releasing actions may provide a mechanism which could be involved in the development of MH.

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# AN EARLY MARKER OF HYPEROXIC LUNG INJURY IN THE RAT AND ITS PHARMACOLOGICAL MODULATION

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## SUMMARY

*Of three possible early biochemical changes which were investigated in rats after hyperoxia, one was shown to be a useful marker of damage in this species. Mitochondrial oxygen uptake measured in lung homogenates has already been reported to be impaired after 24 h. With a purified mitochondrial fraction, we found significant impairment after only 3 h exposure to 100% oxygen. To our knowledge, this is the earliest significant change reported in this species. The antioxidants N-acetyl cysteine, dimethyl sulphoxide and allopurinol were found to ameliorate the injury. This suggests a possible link with the pulmonary damage and survival of rats in hyperoxia, which may be modulated also by antioxidant therapy.*

**KEY WORDS**
*Lung damage Oxygen: toxicity.*

Exposure of patients to high concentrations of oxygen is routine in many situations including intensive therapy, anaesthesia, radiotherapy and diving. Such exposure is known to cause serious lung injury in laboratory animals. Pleural effusion, increased lung capillary permeability and pulmonary oedema are detectable in the rat from about 48 h exposure to 100% oxygen [1–3].

There is evidence that hyperoxia increases production of both the superoxide free radical and hydrogen peroxide in isolated mitochondria *in vitro* [4, 5]. Antioxidant induction or therapy has been found to increase survival times [6–8] and reverse changes in lung permeability (assessed by $^{125}$I-albumin flux) in rats exposed to 100% oxygen [3]. However, such studies investigate events late in hyperoxic exposure and cannot represent the primary biochemical changes. The aim of the present study was to investigate possible early markers of damage in hyperoxia. This should help in defining the nature of early injury and be useful in the development of effective prophylactic measures. In addition (if the technique could be applied in patients) it would provide a basis for early diagnosis of hyperoxic lung injury.

Three studies have reported biochemical changes in the first 24 h of exposure to hyperoxia. In the first, lung homogenates from rats exposed to 100% oxygen for 24 h showed reduced uptake of oxygen (in the presence of succinate and ADP) compared with homogenates from control animals [9]. In the second, when rabbits underwent ventilation with an increased $F\text{I}_{\text{O}_2}$ for 30 min, the lung microsomal phospholipid fatty acid composition was found to be significantly altered [10]. In the third, acid precipitable hydroxyproline was reported to be significantly increased in endobronchial washings from rats after 24 h exposure to 100% oxygen [11]. These reports led us to explore further the use of these techniques (and their derivatives) as potential early markers of hyperoxic injury. We measured oxygen uptake by purified lung mitochondrial fractions, mitochondrial and microsomal phospholipid fatty acid compositions and hydroxyproline concentrations in endobronchial washings. Significant biochemical changes within 24 h exposure were followed up by experiments to determine if these changes could be modulated by antioxidant therapy. Of the four compounds used, N-acetylcysteine and dimethylsulphoxide are predominantly hydroxyl radical scavengers. Allopurinol is also an inhibitor of xanthine oxidase, which is a source of the superoxide radical. Desferrioxamine owes much

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of its antioxidant capacity to its metal chelation properties.

## MATERIALS AND METHODS

### *Oxygen exposures*

Rats (female Sprague–Dawley, 160–200 g body weight) were exposed to 100% oxygen or air in a large Perspex container into which a conventional cage containing six animals could be placed [3]. Oxygen or air was delivered at 15 litre $min^{-1}$. Slight positive pressure (2–3 cm $H_2O$) was maintained to prevent ingress of air. Exposure was for a maximum of 60 h and the animals showed no sign of respiratory (or other) distress. A 12-h light and dark schedule was maintained and rats were allowed diet and water *ad libitum*.

### *Lung mitochondrial oxygen uptake*

Groups of rats were exposed to oxygen or air for 0, 3, 24 or 48 h. Rats were then anaesthetized with halothane and killed by cervical dislocation. Lungs were removed and placed in 10 ml of ice-cold buffer (sucrose 0.225 mol $litre^{-1}$, potassium phosphate 10 mmol $litre^{-1}$ pH 7.4, magnesium chloride 5 mmol $litre^{-1}$ and triethanolamine 20 mmol $litre^{-1}$ pH 7.4) and were homogenized using a Silverson laboratory emulsifier at maximum speed for 30 s. Homogenates were centrifuged initially at 600 *g* for 10 min, the supernatants were transferred and centrifuged further at 10000 *g* for 10 min. The mitochondria-rich pellets were resuspended in 1 ml of buffer, equilibrated with air at 37 °C. Oxygen uptake rates were determined with a Clarke electrode. A background rate was recorded with 500 µl of mitochondrial fraction made up to 3.5 ml with buffer. State 3 (ADP stimulated) respiration was recorded by adding final concentrations of sodium succinate 3.3 mmol $litre^{-1}$ and ADP 0.3 mmol $litre^{-1}$. Rates of uptake of oxygen per minute were related to total lungs (lung wet weight, dry weight and protein can all change in oxygen exposure).

### *Lung mitochondrial and microsomal phospholipid fatty acid composition*

Groups of rats were exposed to oxygen or air for 1 h or 24 h. Mitochondrial fractions were prepared as described above. Microsomal fractions were prepared by centrifuging the supernatant from the 10000 *g* spin at 100000 *g* for 1 h (at 4 °C). Both fractions were resuspended finally in 500 µl of buffer. Lipids were extracted by adding 5 ml of chloroform–methanol (2:1 by volume) containing butylated hydroxytoluene 10 mg $litre^{-1}$. The mixtures were shaken for 10 min and centrifuged at 1000 *g* for 10 min. The upper (chloroform) layer was transferred and evaporated. The extracted lipids were taken up in chloroform 250 ml. The extract was applied (50 µl in a 1-cm band) to a thin layer chromatography plate (Analtech, silica gel G, 250 µm) and developed with a mobile phase of hexane–diethyl ether–acetic acid (80:20:2 by volume). Solvent was evaporated from the plate and visualized by brief exposure to iodine vapour. Lipid classes were identified by comparisons of migrations with those of authentic standards. The phospholipid spot (origin) was transferred to a screw-cap tube for esterification. Methanolic sodium hydroxide (400 µl of 0.5 mol $litre^{-1}$) was added and the capped tubes were heated at 100 °C for 5 min. Boron trifluoride reagent 500 ml (Sigma) was added and the tubes heated at 100 °C for a further 2 min. The methyl esters were extracted into hexane and analysed with a Pye-Unicam 204 gas chromatograph.

### *Acid precipitable hydroxyproline in endobronchial washings*

Groups of rats were exposed to oxygen or air for 0, 24, 48 or 60 h. At the end of the exposure rats were anaesthetized by i.p. injection of pentobarbitone 30 mg (Sagatal). The thorax was opened and a cannula was tied into the trachea. The heart and lungs were removed intact and bathed in warm physiological saline. The contents of the lungs were washed out with saline 2 ml. This was repeated twice and the three washings were pooled and centrifuged at 600 *g* for 10 min. The supernatants were added to concentrated hydrochloric acid (HCl) 3 ml. The mixture was centrifuged at 1500 *g* for 30 min. The pellet was taken up in water 2 ml, added to a further 3 ml of concentrated HCl and hydrolysed by heating at 116 °C for 16 h in a screw-cap culture tube. Hydroxyproline was assayed by oxidation to pyrrole and reaction with p-dimethylaminobenzaldehyde to form a complex quantifiable photometrically (absorption at 560 nm) [12].

### *Antioxidant administration*

Four groups of rats were prepared for each antioxidant tested. Both antioxidant-treated and control animals were exposed to oxygen or air for 24 h. Treatment with each antioxidant was started

TABLE I. *Oxygen uptake by mitochondrial fractions from lungs of rats exposed to 100% oxygen or air (mean* (SD)) (n = 6). *Significant differences after 3, 24 and 48 h exposure.* *P < *0.05;* **P < *0.01;* ***P < *0.001*

| | Oxygen uptake (nmol $min^{-1}$/lungs) | | | |
|---|---|---|---|---|
| | 0 h | 3 h | 24 h | 48 h |
| 100% oxygen | — | 78.6 (15.3)<br>* | 65.4 (9.6)<br>** | 67.8 (18.3)<br>*** |
| Air | 96.0 (9.9) | 98.4 (12.9) | 88.2 (7.5) | 99.6 (11.1) |

TABLE II. *Fatty acid composition of lung microsomal phospholipid from rats exposed to 100% oxygen or air (mean* (SD)) (n = 6). *No significant difference between oxygen-exposed and control animals*

| | Fatty acid (% of total recovered) | | | |
|---|---|---|---|---|
| | 1 h | | 24 h | |
| Fatty acid | 100% $O_2$ | Air | 100% $O_2$ | Air |
| 16:0 | 33.7 (0.5) | 31.7 (1.3) | 31.8 (0.9) | 30.6 (1.4) |
| 18:0 | 11.4 (0.2) | 11.6 (0.5) | 13.4 (0.9) | 15.1 (0.6) |
| 18:1 | 14.3 (0.6) | 14.3 (0.5) | 14.9 (0.5) | 15.6 (0.6) |
| 18:2 | 7.3 (0.2) | 7.6 (0.4) | 7.1 (0.4) | 8.0 (1.6) |
| 20:4 | 15.2 (0.3) | 14.4 (0.4) | 12.3 (0.6) | 11.1 (1.4) |
| 20:5 | 1.1 (0.2) | 1.2 (0.2) | 1.1 (0.1) | 1.1 (0.3) |
| 22:6 | 4.0 (0.2) | 4.3 (0.4) | 3.6 (0.1) | 3.1 (0.4) |

12 h before and continued throughout exposure. N-acetylcysteine was administered at 3% (w/v) in drinking water adjusted to pH 7.0 with sodium bicarbonate. Desferrioxamine was given by i.p. injection (20 mg every 12 h), controls being injected with an equivalent volume of saline. Dimethyl sulphoxide was given at 1.5% (w/v) in drinking water. Allopurinol was given at 25 mg/100 g of powdered diet, controls having powdered diet alone. Food and water were taken normally during the first 24 h of exposure to oxygen. Mitochondrial fractions were prepared and oxygen uptake measured as described above.

### *Statistical analysis*

Data were analysed by one-way analysis of variance and then two-sample Student's *t* tests as appropriate. Variances were compared by *F* ratio and were not significantly different. $P < 0.05$ was considered significant.

## RESULTS

### *Oxygen uptake*

Oxygen uptake by the mitochondrial fraction in the presence of succinate and ADP (state 3) was significantly reduced after 3, 24 and 48 h exposure to 100% oxygen (table I). The 20% reduction at 3 h was significant at the 2% level. After 24 and 48 h the reductions were 26% and 32%, respectively.

### *Fatty acid composition*

Phospholipid from rat lung microsomal and mitochondrial fractions was analysed for fatty acid composition. No significant differences were found between data from rats exposed to 100% oxygen (for 1 h or 24 h) and control animals (tables II and III).

### *Hydroxyproline*

The mean acid precipitable hydroxyproline content of endobronchial washings from rats exposed to 100% oxygen was greater than that from control animals (table IV). There was a trend of increased hydroxyproline content throughout oxygen exposure. However, there was considerable scatter among the data and a statistically significant difference was not reached until 60 h.

### *Antioxidant therapy*

Three compounds afforded significant protection of mitochondrial function in rats exposed to

TABLE III. *Fatty acid composition of lung mitochondrial phospholipid from rats exposed to 100% oxygen or air (mean (SD)) (n = 6). No significant difference between oxygen-exposed and control animals*

| | Fatty acid (% of total recovered) | | | |
|---|---|---|---|---|
| | 1 h | | 24 h | |
| Fatty acid | 100% $O_2$ | Air | 100% $O_2$ | Air |
| 16:0 | 29.3 (1.9) | 32.4 (2.0) | 32.4 (2.5) | 32.7 (2.6) |
| 18:0 | 12.3 (1.7) | 10.7 (0.4) | 13.5 (2.2) | 13.2 (0.2) |
| 18:1 | 12.3 (1.5) | 13.4 (0.6) | 12.6 (1.1) | 14.2 (0.4) |
| 18:2 | 9.5 (0.6) | 9.7 (0.8) | 8.6 (0.6) | 8.0 (0.3) |
| 20:4 | 13.4 (0.8) | 13.5 (0.1) | 12.5 (1.0) | 11.8 (0.6) |
| 20:5 | 1.6 (0.7) | 1.2 (0.2) | 1.9 (0.7) | 1.3 (0.3) |
| 22:6 | 3.8 (0.5) | 4.5 (0.4) | 4.5 (0.8) | 3.4 (0.2) |

TABLE IV. *Acid precipitable hydroxyproline concentration in endobronchial washings from rat lungs after exposure to 100% oxygen or air (mean (SD)) (n = 6). ***Significant difference from air control after 60 h exposure* ($P < 0.001$)

| | Hydroxyproline (μg/lungs) | | | |
|---|---|---|---|---|
| | 0 h | 24 h | 48 h | 60 h |
| 100% oxygen | — | 2.12 (0.71) | 2.50 (1.31) | 3.77 (0.71)<br>*** |
| Air | 1.15 (0.15) | 1.47 (0.43) | 1.32 (0.69) | 1.43 (0.55) |

TABLE V. *Effects of antioxidants on oxygen uptake by mitochondrial fractions from lungs of rats exposed to 100% oxygen or air for 24 h (mean (SD)) (n = 6). Significant difference from oxygen-exposed controls:* *$P < 0.05$; **$P < 0.01$

| | Oxygen uptake (nmol $min^{-1}$/lungs) | | | |
|---|---|---|---|---|
| | Antioxidant treated | | Controls | |
| Treatment | 100% $O_2$ | Air | 100% $O_2$ | Air |
| N-Acetylcysteine | 91.2 (13.8)* | 115.5 (16.8) | 69.0 (12.0) | 109.8 (14.1) |
| Desferrioxamine | 64.2 (4.7) | 102.9 (15.9) | 69.1 (3.7) | 96.7 (14.3) |
| Dimethyl sulphoxide | 85.5 (9.3)** | 115.2 (4.5) | 66.2 (8.6) | 105.1 (16.8) |
| Allopurinol | 87.3 (5.1)* | 115.2 (24.7) | 70.6 (8.6) | 114.1 (4.0) |

100% oxygen (table V). At the doses given, N-acetylcysteine achieved 54% protection, dimethyl sulphoxide 50% and allopurinol 38%; desferrioxamine gave no protection. Despite these various degrees of protection, all oxygen-exposed and antioxidant-treated groups had mitochondrial oxygen uptake rates significantly less than those in air breathing controls.

## DISCUSSION

Currie, Pratt and Sanders [9] reported that state 3 oxygen uptake in lung homogenates was significantly reduced after rats had been exposed to 100% oxygen for 24 h. Uptake was reported to be further reduced at 48 h, and then stabilized at this lower value for up to 7 days exposure. Using a mitochondrial fraction, we have found a significant change as early as 3 h after the start of hyperoxic exposure. The rate of uptake appears to stabilize a little earlier (in our experiments) than was reported by Currie's group, and it is possible that these authors did not achieve 100% oxygen in their exposures. Indeed, the fact that their rats survived for up to 7 days suggests that the concentration of oxygen was substantially less than 100%, in which rats do not usually survive beyond the 4th day of exposure.

Bassett and colleagues [13, 14] have studied pyruvate and glucose metabolism in isolated perfused lungs from oxygen-exposed rats and have suggested that the mitochondrial pyruvate dehydrogenase complex is a likely site of inhibition. It has long been proposed that the initial biochemical event in oxygen toxicity is the generation of oxygen-derived free radicals [15]. Clearly, mitochondria are a likely site for such reactions. Leakage of single electrons from the respiratory chain to oxygen is likely to be increased in hyperoxia. Mitochondrial enzymes are, therefore, likely targets for free radical reactions, as free radical species are often highly reactive and therefore react in the immediate locality of their formation.

Casals and colleagues [10] have reported various changes in the microsomes from lungs of rabbits which had undergone ventilation with high oxygen concentrations for only 30 min. Among the most striking of these were changes in fatty acid composition. We could find no changes in microsomal or mitochondrial fatty acid composition in lungs of rats exposed to 100 % oxygen. Clearly, the two sets of experiments are not directly comparable, as there is a difference in species and experimental procedure. We can only conclude that changes in fatty acid composition are unlikely to be a useful marker of hyperoxic injury in the rat.

There is disagreement in the existing literature regarding hydroxyproline in endobronchial washings. Valimaki and Niinikoski [11] reported a very striking increase after 24 h exposure to 90–95 % oxygen, while Riley and colleagues [16] detected no increase before 2.8 days. Our data are similar to those of the latter group, in that no significant increase could be detected before 60 h. Valimaki and Niinikoski [11] published in 1973 and to our knowledge their finding has not been confirmed. It would seem that endobronchial hydroxyproline is not a reliable marker of early damage in hyperoxia.

A reported early marker of oxidative lung injury, which has not been considered in the present study, is the reduction of serotonin uptake by lungs [17]. However, it has been suggested that this is secondary to the impairment of mitochondrial function [14], as such uptake requires mitochondrial energy production [18]. It would be interesting to make a careful comparison of the time courses of these two changes.

To our knowledge, this paper contains the first study of antioxidant modulation of an early marker of lung injury in hyperoxia. Up to 54 % protection of mitochondrial function was achieved. Further work is required to determine if other compounds, routes of administration, doses or combinations of drugs could improve on this finding. The negative result with desferrioxamine is difficult to interpret, as it may simply indicate that the compound failed to reach the appropriate site for its action. Clearly, the positive findings with three antioxidants are consistent with a role for free radicals in the early stage of hyperoxia-dependent impairment of mitochondrial function. However, it must be stressed that they do not prove such a role, as such compounds may have various modes of action. Whatever the mechanism of protection, the findings are suggestive of a possible link between the impairment of mitochondrial function and the long term survival of rats in hyperoxia, which is also responsive to antioxidant therapy. N-Acetylcysteine and other thiols are known to be effective in this role [7], as are catalase and superoxide dismutase [8]. N-Acetylcysteine protected also against increased lung capillary permeability [3]. Dimethyl sulphoxide has shown significant protection against the appearance of pleural effusion [3]. Any link between mitochondrial function and later damage may not be causative, since both phenomena could derive from some other event. Nonetheless, the very early occurrence of the reduction in uptake of oxygen (within the first 3 h of hyperoxia and long before any overt signs of damage) suggests that it is close to the primary events in hyperoxic lung injury.

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# NON-STEROIDAL ANTI-INFLAMMATORY DRUGS: RATIONALE FOR USE IN SEVERE POSTOPERATIVE PAIN

J. B. DAHL AND H. KEHLET

Relief of postoperative pain after abdominal and orthopaedic surgery is provided traditionally by parenteral opioid analgesics or local anaesthetic regimens. We have emphasized previously that total postoperative pain relief cannot be achieved by a single agent or method without major expenditure on equipment and surveillance systems or without significant side effects [38], and therefore recommended combined analgesic regimens (balanced analgesia) or a multimodal approach to the treatment of postoperative pain [16, 38].

Recent information on the role of arachidonic acid cascade metabolites to mediate pain and inflammation at the site of peripheral pain suggests that pharmacological modulation of the arachidonic acid cascade may be of value in the "balanced analgesia" approach to postoperative pain. Non-steroidal anti-inflammatory drugs (NSAID) have proved reliable in relieving postoperative pain after minor procedures such as dental surgery [18, 56] and episiotomy [57], and recent studies suggest that NSAID may have an important role as adjuvants to other analgesics after major surgery.

This review describes the role of prostaglandins in pain and inflammation and discusses the effects of NSAID on postoperative pain after major surgical procedures and their potential side effects.

## PERIPHERAL EVENTS IN TISSUE TRAUMA AND POSTOPERATIVE PAIN

Tissue injury leads to *nociception* by direct mechanical and thermal damage to nerve endings, to *inflammation* by the release of chemicals and enzymes from nerves and damaged tissue and to *hyperalgesia* generated by algogenic substances and "sprouting" of damaged nerves into the injured tissue [14, 60].

After noxious stimuli to peripheral nerves, antidromic impulses in axons promote the release of substance P from nerve endings, resulting in vasodilatation and increase in vascular permeability. This causes local oedema and, in combination with release of algogenic substances (e.g. prostaglandins, leucotrienes, bradykinin, serotonin and histamine), leads to inflammation and sensitization of nociceptors, resulting in hyperalgesia. The primary afferent neurone thus serves a dual function: transmission of neural stimuli and peripheral release of mediators of inflammation at the site of trauma [42]. Activation of nociceptive afferents may also elicit spinal cord reflexes that markedly increase the activity of postganglionic sympathetic efferents. Various agents, including noradrenaline and dopamine, stimulate synthesis of cellular phospholipids by releasing non-esterified free fatty acid precursors, and thus release of prostanoids and leucotrienes [78]. The sympathetic efferents may, therefore, directly or indirectly, increase vascular permeability and leucocyte infiltration in addition to other factors, and amplify the inflammation [42].

Hyperalgesia is an altered functional state of the nervous system characterized by a decrease in pain threshold, an increase in pain to suprathreshold stimuli and often spontaneous pain. *Primary hyperalgesia* refers to changes that occur within the site of injury and *secondary hyperalgesia* to changes in the surrounding area (fig. 1). Primary

***KEY WORDS***

*Analgesics: non-steroidal anti-inflammatory drugs. Pain: postoperative.*

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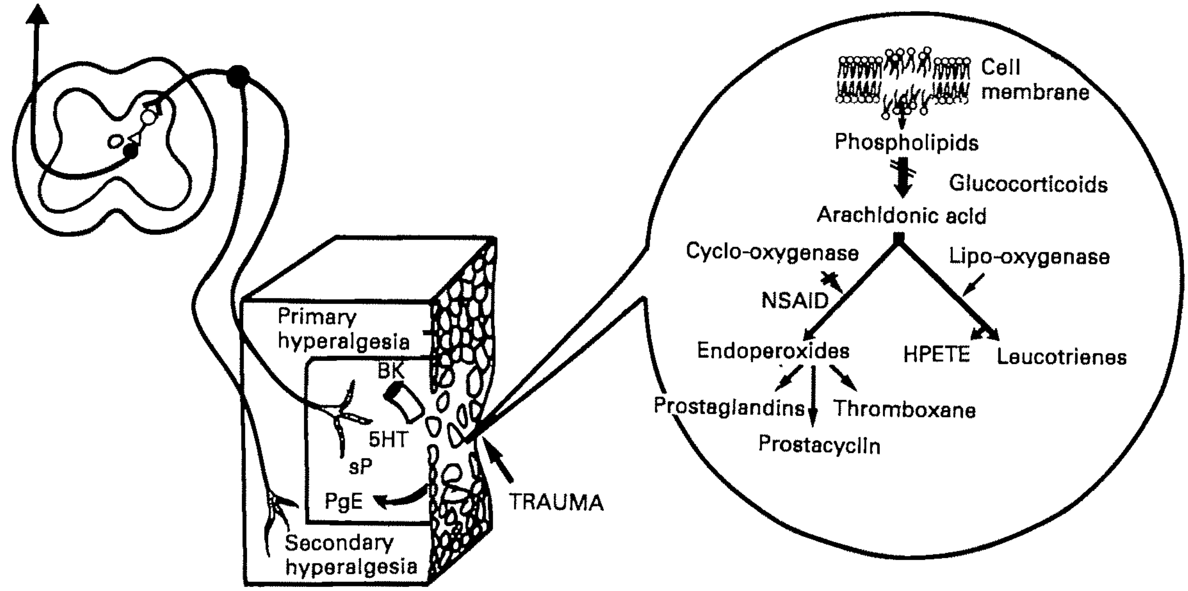

FIG. 1. Tissue injury leads to release of substance P (sP) from nerve endings and release of algogenic substances (e.g. bradykinin (BK), serotonin (5HT), histamine and arachidonic cascade metabolites) resulting in vasodilatation, increase in vascular permeability and sensitization of nociceptors (primary hyperalgesia). Secondary hyperalgesia results probably from functional changes in both the peripheral and central nervous system. Arachidonic acid can be metabolized to the prostaglandin endoperoxides (PgE) by the enzyme cyclo-oxygenase or to hydroperoxy derivatives (HPETE) and leucotrienes by the lipo-oxygenase pathway. NSAID inhibit the biosynthesis of prostaglandins by means of an acetylation and consequent inactivation of cyclo-oxygenase.

hyperalgesia may be explained by sensitization of nociceptors. Secondary hyperalgesia probably results from changes both in the peripheral and central nervous system [60].

*Prostaglandins, NSAID and nociception*

Evidence has accumulated that bradykinin and the products of arachidonic acid metabolism promote the pain and hyperalgesia associated with inflammation. This may be a result of potentiation of bradykinin effects by prostaglandins [37, 60] and bradykinin itself may stimulate synthesis and release of prostaglandins by activation of phospholipase A [60]. With the exception of non-nucleated erythrocytes, all other cells are capable of synthesizing prostaglandins, which are released in response to trauma or disturbance of the cell membrane [75]. Arachidonic acid, the precursor of prostaglandins, prostacyclins and thromboxanes, may be metabolized to the prostaglandin endoperoxides by the enzyme cyclo-oxygenase, or to hydroperoxy derivatives by the lipo-oxygenase pathway (fig. 1). In experimental studies, prostaglandins have been detected in inflammatory exudates in the skin and synovial fluid, and in exudates from joints from human rheumatoid arthritis sufferers [60].

Salicylates inhibit the biosynthesis of prostaglandins by irreversible acetylation and consequent inactivation of cyclo-oxygenase, in contrast with other NSAID which are reversible inhibitors [40]. Paracetamol blocks brain prostaglandin synthetase *in vitro*, but not that of peripheral tissue and is antipyretic but not anti-inflammatory [40]. Experimental studies suggest further that indomethacin and some other NSAID interact with the adenylate cyclase system by inhibition of phosphodiesterase [77], thereby increasing the intracellular concentration of cyclic AMP. Cyclic AMP has been shown to stabilize membranes in polymorphonuclear leucocytes, thus reducing the release of enzymes known to play a role in the inflammatory response [77]. In addition, generation of superoxides by phagocytes may be decreased by cyclic AMP. Thus the pain relieving effect of NSAID may be explained by several mechanisms, including inhibition of prostaglandin biosynthesis [40]. Failure to respond clinically to NSAID is not unusual in the treatment of rheumatoid arthritis and it has been proposed that NSAID may have different effects on the various prostaglandin synthetase enzymes in responders compared with non-responders [4].

With the inhibition of cyclo-oxygenase by NSAID, more arachidonic acid may be released for metabolism by the lipo-oxygenase pathway, partly because the prostaglandin cyclo-oxygenase pathway is closed, and partly because some prostaglandins normally may inhibit release of arachidonic acid from phospholipids by a mechanism involving cyclic adenosine monophosphate [48]. Some of the lipo-oxygenase products may be important in recruiting leucocytes to the inflammatory site and to release lytic enzymes involved in tissue damage and inflammation [75]. This may explain the osteoarthritis-provoking activity of some NSAID in experimental studies [48].

NSAID may also have central effects on nociception, although the mechanisms have not been clarified [36].

### *Physiological effects of inhibition of cyclo-oxygenase*

Prostaglandins have important effects on gastric and renal physiology, and possess a haemostatic function.

Prostaglandins may inhibit gastric acid secretion and stimulate the production of mucus. Blood flow in the gastric mucosa is reduced by inhibitors of prostaglandin synthesis, which may lead to damage in relatively ischaemic areas [65]. Prostaglandins may also increase the migration of basal cells toward the lumen to repair mucosal injury [65]. It has been argued that the ulcers associated with NSAID are different from ordinary ulcers and the term non-steroidal anti-inflammatory gastropathy has been proposed for this disease [28, 65]. Ulcers in patients taking NSAID are often silent and are part of a spectrum of disease that includes erosions and petechiae [28]. The influence of route of administration on gastroduodenal damage is still debatable. Thus the ulcerogenicity of rectally administered NSAID may not be related directly to the degree of inhibition of prostaglandin $E_2$ synthesis [43]. Intra-arterial infusion of some leucotriene derivatives may increase ethanol-induced gastric damage by a reduction in vascular perfusion [76].

Endogenous prostaglandins may exert little influence on renal function in the basal state, but are important modulators of renal haemodynamics in states of decreased perfusion. Thus NSAID may cause a decrease in glomerular filtration rate and release of renin from juxtaglomerular granular cells, and an increase in renal vascular resistance which may lead to renal insufficiency, hyperkalaemia and sodium and water retention [12, 17].

The formation of thromboxanes and prostaglandins is essential for normal human haemostasis. Both prostaglandin endoperoxides and thromboxane $A_2$ induce rapid and irreversible aggregation of human platelets [52]. Although most cells can synthesize new cyclo-oxygenase, platelets cannot. Because the inactivation of cyclo-oxygenase by salicylates is irreversible, its effect on bleeding time is prolonged (12–15 days) and more complex than those of other NSAID. The other NSAID are reversible inhibitors and inhibit platelet aggregation only as long as they remain in the circulation [15, 40].

Finally, recent studies suggest that NSAID reduce cerebral blood flow [22], but most data are derived from infants and the potential role of this observation for the surgical patient is unclear.

### *Effect of NSAID on the systemic response to surgery*

Surgical trauma and endotoxin administration lead to a well-described systemic response with hypermetabolism, hyperthermia, leucocytosis and acute phase protein response, immunosuppression, catabolic hormone secretion and negative nitrogen balance. The arachidonic cascade metabolites may play an important role in mediating these responses, as clinical studies have demonstrated that NSAID modify several aspects of the injury response. Thus indomethacin may reduce hyperthermia and nitrogen excretion [38] and improve immunosuppression [25] after surgery. Ibuprofen pretreatment may reduce the increase in 6-keto-PGF1$\alpha$ and $TxB_2$ and the prostacyclin-mediated haemodynamic changes that occur in association with abdominal aortic surgery [32]. Finally, ibuprofen may reduce the hypermetabolic and endocrine responses, tachycardia and fever, but not leucocytosis and acute phase protein response following administration of endotoxin [62]. These findings suggest a potentially valuable role of NSAID in surgery and acute care therapy [64], but there is a need for larger controlled

TABLE I. *Effect of NSAID* vs *placebo on postoperative pain and opioid requirements following abdominal surgery. Dose–response data or data from comparisons with other NSAID or opioids not included*

| | | | | | Effect on | |
|---|---|---|---|---|---|---|
| Ref. | NSAID | Method of administration | Time of (first) administration | Type of surgery | Pain intensity | Opioid requirement |
| [9] | Diclofenac | I m., one dose | 30 min *postop.* | Hysterectomy | ↓ | ↓ |
| [30] | Diclofenac | I.m., two doses | "Immediately" *postop.* | Abdominal | → | ↓ |
| [74] | Diclofenac | I.v., one dose | At wound closure | Abdominal + "superficial" | → | → |
| [13] | Diclofenac | Rectal, one dose | "Immediately" *postop.* | Cholecystectomy | → | → |
| [61] | Indomethacin | Rectal/8 h in 72 h | *Postop.*, first request | Upper + lower abdominal | ↓ | ↓ |
| [73] | Indomethacin | Rectal/8 h in 72 h | 16 h *preop.* | Upper + lower abdominal | ↓ | ↓ |
| [23] | Indomethacin | I.v. bolus + rectal/ 8 h in 72 h | "Immediately" *preop.* | Hysterectomy | ↓ | ↓ |
| [24] | Ketorolac | I.m., one dose | 1 day *postop.* | "Abdominal" | ↓ | ? |
| [27] | Ketorolac | I.v. infusion in 24 h | "Immediately" *postop.* | Upper abdominal | ↓ | ↓ |
| [55] | Ibuprofen | Rectal/8 h in 24 h | 60–90 min *preop.* | Lower abdominal (hysterectomy) | → | ↓ |
| [63] | Indoprofen | I.v. infusion in 2 h | *Postop.*, first request | Upper + lower abdominal | ↓ | ? |
| [68] | Piroxicam | Oral, one dose | *Postop.*, first request | Upper + lower abdominal | ↓ | ↓ |
| [19] | Naproxen | Oral, one dose | 30 min *preop.* | Herniotomy | ↓ | ↓ |

studies before the clinical implications of such therapy can be assessed.

No systematic studies on a potential differential effect between the various NSAID on the systemic response to injury are available.

## CLINICAL STUDIES ON THE EFFECTS OF NSAID ON PAIN FOLLOWING MAJOR SURGERY

### *NSAID* vs *placebo*

In 11 of 13 studies in upper or lower abdominal surgery (or both), pain intensity or opioid requirement (or both) were reduced significantly by NSAID compared with placebo (table I). Results have been consistent despite the use of different drugs and different schedules of administration. The opioid sparing effect has been reported to vary between 20% [55] and 35% [19]. In two studies with diclofenac, no significant effect of NSAID compared with placebo could be demonstrated [13, 74]. These results may be a reflection of the limited number of patients investigated compared with all other studies in table I; in two studies with more patients included, diclofenac showed a significant pain relieving effect [9, 30].

In six studies in orthopaedic surgery [3, 6, 31, 44, 67, 71], pain intensity, opioid requirement, or both were reduced significantly in patients receiving diclofenac, indomethacin, indoprofen, piroxicam or ketorolac compared with placebo (table II), although the effect of ketorolac on post-meniscectomy pain was modest [31].

### *NSAID* vs *opioids*

The effect of lysine acetylsalicylate (LAS), a soluble salt of acetylsalicylic acid, has been compared with that of opioid in the treatment of postoperative pain after various major surgical procedures [11, 34, 41, 45, 72]. No significant differences were found between the speed of action or degree of pain relief in the first 6 h after injection of LAS 1.8 g compared with morphine 10 mg after major gynaecological surgery [41]. Constant i.v. infusion of LAS 1.8 g 6-hourly provided analgesia equivalent to that of constant i.v. infusion of morphine 10 mg 6-hourly after both herniotomy [11] and thoracic surgery [34]. In the latter study, however, the patients were able to self-administer incremental doses of papaveretum from a patient-controlled analgesic device and the use of papaveretum was not

TABLE II. *Effect of NSAID vs placebo on postoperative pain and opioid requirements following orthopaedic surgery. Dose–reponse data or data from comparisons with other NSAID or opioids not included*

| Ref. | NSAID | Method of administration | Time of (first) administration | Type of surgery | Effect on: Pain intensity | Effect on: Opioid requirement |
|---|---|---|---|---|---|---|
| [44] | Diclofenac | I.m., one dose | 1 day *postop.* | Hip arthroplasty | ↓ | ? |
| [71] | Indomethacin | I.v. infusion in 20 h | "Immediately" *preop.* | Ankle, knee | ? | ↓ |
| [3] | Indoprofen | I.v., one dose | At wound closure | Hip, knee and other | ↓ | ? |
| [31] | Ketorolac | Oral/4–11 h in 120 h | 1 day *postop.* | Meniscectomy | ↓ (→) | ? |
| [6] | Piroxicam | Oral, one dose | 1 day *postop.* | Orthopaedic | ↓ | ↓ |
| [67] | Piroxicam | Oral/24 h in 72 h | *Preop.* evening | Hip arthroplasty | → | ↓ |

statistically different in patients who received LAS compared with morphine [34]. The result of this study, therefore, is merely a demonstration of an opioid-sparing effect of LAS. In a single-dose study following upper abdominal surgery [72], it was suggested that LAS 1.8 g may be substituted for about 6 mg of oxycodone. In another study [45], single injection of LAS 1.8 g after gynaecological or orthopaedic surgery did not provide effective or consistent relief of pain. From these studies [11, 34, 41, 45, 72] it may be concluded that i.v. salicylate alone seems of some value in the alleviation of postoperative pain, provided that the pain is not severe. More relevant in the present context is the observation that LAS seems to possess an opioid-sparing effect after major surgery.

In several other studies, various NSAID have been compared with opioids [26, 50, 53, 66, 79]. However, interpretation of the results are difficult because of ill-defined methods of assessment and major differences in surgical procedures between the patients studied. The aetiology of pain seems to be an important factor in trial design and major surgery may provide a more sensitive assay of analgesic efficacy [8]. In a recent study, inadequacy of smaller doses of morphine compared with NSAID was clearly apparent in patients undergoing major surgery, in contrast with patients who underwent minor surgical procedures [79]. In the most recent and well-conducted studies of the effects of NSAID compared with opioid, however, ketorolac 30 mg given up to 2-hourly on patient demand after upper abdominal surgery (cholecystectomy), produced significantly less analgesia than morphine 10 mg on the first day after operation [59]. Furthermore, patients receiving ketorolac required repeated analgesic sooner and more rescue medication than the morphine group [59]. In patients who received ketorolac 10 mg or morphine 10 mg after lower abdominal (gynaecological) surgery [58], pain scores were similar in the two groups, but pain relief scores were better in the morphine group. Pain scores on a four-point verbal scale (none–mild–moderate–severe) had a median value of moderate (range mild–severe) in both groups throughout the study [58], indicating that neither regimen was effective in relieving severe pain. This is in accordance with results from most of the placebo-controlled studies in major surgery, where rather small opioid sparing effects (about 30%) have been demonstrated (see above). Thus results from studies of the effect of NSAID on severe postoperative pain gives no reason to believe that these drugs provide adequate analgesia when used as the sole agent, and most patients may require additional opioids or other regimens [39].

## COMBINATION REGIMENS

Relief of postoperative pain after abdominal and orthopaedic surgery is provided traditionally by single-drug regimens, but combinations of different regimens (e.g. extradural local anaesthetic and opioid) have been suggested to be more rational and effective [38]. The argument for the use of a combination of analgesics is that drugs acting by different mechanisms result in additive or synergistic analgesia [16]. Opioids act on specific opioid receptors in the CNS to attenuate the pain-related signals, while NSAID act mainly in the periphery to inhibit the initiation of pain signals interfering with prostaglandin synthesis after tissue injury (fig. 1).

From this, it seems obvious that NSAID may be valuable as adjuvants to other analgesics after major surgery. The aim of these combinations should be to achieve additive–synergistic effects with reduction in postoperative pain, rather than to reduce the need for opioids *per se*. Optimal composition of combined drug regimens may therefore, at least theoretically, reduce the need for each constituent, with a concomitant reduction in adverse effects. There is substantial evidence that combinations of an optimal dose of NSAID with an opioid produce an additive analgesic effect greater than that obtained by doubling the dose of each constituent administered alone [5, 46, 69] and improved pain relief combined with a reduced need for central acting analgesics has been obtained by adding NSAID to a conventional opioid regimen during total hip joint replacement [35]. In a recent study of postoperative pain following major abdominal surgery, however, no effect of supplementary piroxicam (20 mg daily) compared with placebo could be demonstrated during an otherwise very effective regimen with continuous extradural infusion of bupivacaine and morphine [49].

In summary, the available data and theoretical background suggest that inclusion of NSAID in a multimodal treatment of postoperative pain (balanced analgesia) may be valuable. However, more data are needed before specific recommendations may be proposed.

## DOSAGE AND DRUG ADMINISTRATION

*Pre*treatment with a drug which interferes with initiation of pain in the periphery should minimize the activation and sensitization of peripheral nociceptors, thereby minimizing the noxious input into the central nervous system and attenuate the inflammatory response normally observed after surgical trauma. Unfortunately, only a few studies have examined the issue of *pre- vs post*operative treatment with NSAID and most studies have used postoperative initiation of NSAID therapy (tables I, II). One controlled study suggested improved analgesia when flurbiprofen was given before rather than after surgery [21]. Oedema and inflammation have been reduced with preoperative administration of NSAID compared with placebo after plastic surgery [29] and rheumatoid surgery [70], while no effect on oedema of external genitalia was observed after bilateral herniorrhaphy [33].

In a few studies, the effects of different NSAID have been compared [1, 47, 54], but without definite conclusions. It is outside the scope of this review to discuss the pharmacokinetics and pharmacodynamics of individual NSAID. Ease of administration (oral, i.v., suppositories) and cost are factors which may also influence choice of drug.

## SIDE EFFECTS

Adverse reactions to NSAID may result from inhibition of cyclo-oxygenase, or toxic or idiosyncratic reactions. The most common side effects of NSAID are gastritis, peptic ulceration and depression of renal function. Other adverse effects of NSAID include blood dyscrasias, dermatological, pulmonary and hepatic reactions and anaphylaxis, but most of these are extremely rare [51, 52]. However, the risk and incidence of side effects of NSAID in the perioperative period are less well known. Idiosyncratic allergic reactions cause dermatological manifestations including urticaria and anaphylactoid reactions resembling hereditary angioneurotic oedema [51]. Asthma in aspirin-sensitive patients may involve a general lack of prostaglandins, and hypersensitivity reactions to aspirin in these patients may be dependent on inhibition of prostaglandins, which may explain cross-reactions with other NSAID [51].

Several studies suggest that the first few months of taking a NSAID may be the most dangerous in respect of gastrointestinal side effects [28], but the data do not allow separation of risk between the first 4–6 days compared with the following weeks. In a retrospective cohort study of 91770 *non-operated* subjects exposed or unexposed to NSAID, the relative risk for developing upper gastrointestinal bleeding 30 days after exposure was 1.5, as upper gastrointestinal bleeding occurred in 0.33% of subjects exposed and 0.22% of subjects not exposed to NSAID. Advancing age, sex, alcohol-related conditions, anticoagulants, and pre-existing abdominal conditions were all associated with upper gastrointestinal bleeding. Patients with a history of upper gastrointestinal tract bleeding were excluded from the study [10]. The risk of gastrointestinal haemorrhage during short-term (1-week) treatment with NSAID is unknown. In the surgical patient, short-term treatment did not lead to major gastrointestinal side effects in the placebo-controlled studies described in tables I and II, or in studies of various NSAID against opioids. However, none of the studies has focused specifically on these problems, and patients with a history of upper gastrointestinal tract bleeding were excluded from most of the studies.

Vasodilator renal prostaglandins maintain renal blood flow and glomerular filtration rate under clinical conditions accompanied by renal vasoconstriction, and caution has been proposed in the use of cyclo-oxygenase inhibitors in patients undergoing major surgery [12, 20]. Other conditions in which renal function is prostaglandin-dependent and therefore an additional risk factor in the perioperative patient, are arteriosclerotic cardiovascular disease in elderly patients, concurrent diuretic therapy, congestive heart failure and extracellular volume depletion [12, 20]. Although such conditions are not unusual in patients undergoing major abdominal or orthopaedic surgery, most data on this subject are derived from experimental studies or studies in human volunteers [12, 20] and no data are available from prospective studies in perioperative patients (except "unpublished observations" in [39]). Interstitial nephritis induced by NSAID is idiosyncratic and the reaction is very rare [2].

Data from studies on the clinical significance of NSAID on coagulation and bleeding are inconclusive. In the studies by Reasbeck, Rice and Reasbeck [61] and Engel and colleagues [23], a significantly greater incidence of haemorrhagic complications and perioperative blood loss occurred during administration of indomethacin 100 mg every 8 h compared with placebo. In the study by Reasbeck's group, however, different haemorrhagic complications, including mechanical failure (breakage of a suture), were grouped together and overall numbers were small (5/44 in the indomethacin *vs* 0/46 in the placebo group) [61]. Blood loss in the study by Engel and colleagues was determined by measuring the volume in the suction bottles and visually as the loss in swabs and, as pointed out by the authors, must be interpreted cautiously [23]. No differences in perioperative blood loss were reported in the other studies described in table I, but only a few studies have examined this issue specifically. No controlled studies have reported increased blood loss after the use of ketorolac for postoperative analgesia [39]. After thoracic surgery, blood loss was not statistically different in patients who received LAS compared with morphine [34] and in another study, perioperative blood loss in patients undergoing transurethral prostatectomy did not differ significantly in patients who received diclofenac compared with those receiving placebo [7]. No significant differences in blood loss after hip replacement were observed in two studies of diclofenac or piroxicam compared with placebo [44, 67]. In a study in patients undergoing emergency surgery of the lower extremities, mean bleeding time was prolonged in the indomethacin group compared with placebo [71]. Although no abnormal bleeding was observed immediately after operation, at the end of a 20-h infusion, insignificantly more patients bled through their bandages (4/28 *vs* 1/26 in the placebo group) [71].

No differences in the incidence of minor side effects which may be related to the use of NSAID (dyspepsia, diarrhoea, headache, vomiting) have been reported compared with placebo in any of the studies in table I or II.

In summary, the well-known side effects during prolonged use of NSAID may hinder their potential use in the perioperative period. However, data from prospective controlled studies, although limited, do not suggest that short term (< 1 week) NSAID treatment may have clinically significant unwanted effects. Thus the fear of side effects should not limit their use in the surgical patient, but further studies are required in patients potentially at risk.

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# EFFECT OF $H_2$-RECEPTOR ANTAGONIST PRETREATMENT ON VECURONIUM- AND ATRACURIUM-INDUCED NEUROMUSCULAR BLOCK

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## SUMMARY

*Seventy-two patients were studied in a double-blind randomized controlled design to assess the effects of oral administration of cimetidine 400 mg, ranitidine 150 mg or placebo 90 min before anaesthesia on the neuromuscular blocking effects of atracurium 0.45 mg kg$^{-1}$ or vecuronium 0.08 mg kg$^{-1}$. The times to reappearance of T1 (first response in the train-of-four stimulation) and its recovery to 25% of control were 22.5 (SD) 5.2 and 30 (7.1) min, 30 (10) and 43 (15.4) min, and 25.8 (4.1) and 34 (6.2) min, respectively in the vecuronium groups pretreated with placebo, cimetidine and ranitidine, the times following cimetidine pretreatment being prolonged significantly ($P < 0.05$). The respective recovery indices (times for 25–75% recovery of T1) in these three groups were 11.0 (3.5), 17.4 (6.8) and 13.0 (3.9) min. There were no significant differences in any of the variables following ranitidine pretreatment and either neuromuscular blocker or following cimetidine pretreatment and atracurium.*

**KEY WORDS**

*Neuromuscular relaxants: atracurium, vecuronium. Histamine: cimetidine, ranitidine. Interactions (drug).*

Cimetidine and ranitidine are commonly used $H_2$-receptor antagonist drugs which have been recommended for the prevention of the acid aspiration syndrome, particularly in the obstetric patient [1]. There is conflicting evidence about the occurrence of interactions between $H_2$-receptor blocking agents and neuromuscular blocking drugs. Whereas Camp and colleagues [2] noted prolongation of the effect of vecuronium in patients given oral cimetidine, Hawkins and colleagues [3] did not observe any effect. On the other hand, treatment with i.v. ranitidine has been shown to antagonize the effect of atracurium in rats [4]. The present study was designed to investigate the influence of single oral doses of cimetidine or ranitidine on the neuromuscular effects of vecuronium and atracurium.

## METHODS AND RESULTS

Seventy-two adult patients aged 18–65 yr, were included in the study with their informed consent and the approval of the Research Ethics Committee. They were allocated randomly to three groups of 24 each. Patients with obesity, renal or hepatic impairment, or receiving any drugs known to interact with neuromuscular blockers or $H_2$-receptor antagonists were excluded. Premedication consisted of oral diazepam 10 mg, and cimetidine 400 mg, ranitidine 150 mg, or a placebo 90 min before operation. The allocation to $H_2$-receptor or placebo groups was randomized and tablets were dispensed from coded numbered bottles by the nursing staff.

Anaesthesia was induced with thiopentone 3–5 mg kg$^{-1}$ and fentanyl 1–2 μg kg$^{-1}$, and maintained with 70% nitrous oxide and 0.5% halothane in oxygen, and increments of fentanyl 1 μg kg$^{-1}$ as required. All patients were monitored with ECG, non-invasive arterial pressure, temperature and pulse oximetry. Ventilation was adjusted to maintain end-tidal carbon dioxide concentrations of 4.5–5.0%.

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TABLE I. *Mean* (SD) *onset and duration of neuromuscular block* †n = 9; ‡n = 7. *P < 0.05 compared with other groups

| | Placebo ($n$ = 12) | Cimetidine ($n$ = 12) | Ranitidine ($n$ = 12) |
|---|---|---|---|
| Vecuronium | | | |
| Onset time (min) | 0.8 (0.2) | 0.7 (0 1) | 0.8 (0.1) |
| Time to maximum block (min) | 2.1 (0.6) | 2.1 (1.2) | 2 0 (0.3) |
| Time to return of T1 (min) | 22.5 (5.2) | 30 (10.0)* | 25.8 (4.1) |
| Time to 25 % recovery of T1 (min) | 30 (7.1) | 43 (15.4)* | 34 (6.2) |
| Recovery index | 11.0 (3.5)† | 17.4 (6 8)*† | 13.0 (3.9)‡ |
| Atracurium | | | |
| Onset time (min) | 0.7 (0.2) | 0.7 (0.1) | 0.7 (0.1) |
| Time to maximum block (min) | 1 8 (1.1) | 2.4 (0.9) | 1.8 (0.4) |
| Time to return of T1 (min) | 33 5 (6.4) | 33.2 (8.3) | 35.2 (5.9) |
| Time to 25 % recovery of T1 (min) | 43 (6.1) | 44 (10.3) | 43 (8 9) |
| Recovery index | 11.9 (4.1)† | 11.0 (2.2)‡ | 11.9 (4.1)‡ |

After induction of anaesthesia, the ulnar nerve was stimulated percutaneously at the wrist with supramaximal stimuli of 0.2 ms duration, in a train-of-four (TOF) sequence at 2 Hz every 10 s, and the resultant force of contraction of the adductor pollicis muscle measured and recorded using a force displacement transducer and neuromuscular function analyser (Myograph 2000, Biometer Ltd). Following stabilization of control responses, 50 % of the patients in each of the three groups received vecuronium 0.08 mg $kg^{-1}$ and the other 50 % received atracurium 0.45 mg $kg^{-1}$ as a single bolus. The time to onset of effect and maximum block of T1 (first response in the TOF) and its spontaneous recovery to 25 and 75 % of control were recorded. The recovery index was measured as the time between 25 and 75 % recovery.

The results were subjected to analysis of variance and the Tukey HSD modification of the analysis of variance to determine statistical significance.

The patients in the six groups were comparable in their physical characteristics. Neuromuscular data are shown in table I.

There was no difference between groups in the time to onset of effect or the time taken to attain maximum block. The times to reappearance of T1 (30 *vs* 22.5 and 25.8 min) and its recovery to 25 % (43 *vs* 30 and 34 min) were significantly longer ($P < 0.05$) in patients receiving vecuronium after cimetidine pretreatment in comparison with those receiving placebo or ranitidine. The recovery index was also significantly longer in this group (17.4 *vs* 11.0 and 13.0 min, respectively). The times to reappearance of T1 and its recovery to 25 % of control and the recovery indices in those groups receiving atracurium were not significantly different from each other. With the exception of the groups reciving cimetidine, the time to 25 % recovery of T1 was longer in the groups receiving atracurium.

## COMMENT

The results from this study show that cimetidine, but not ranitidine, had a significant influence on the duration of action of vecuronium. These results confirm the findings of other workers using the two $H_2$-receptor antagonists i.v. [5], even though oral administration may achieve smaller peak plasma concentrations than i.v. administration. Previously reported results following cimetidine administration may be conflicting because of the use of insensitive methods of neuromuscular monitoring [2,3].

*In vitro* studies with both cimetidine and ranitidine have shown that in large doses they may produce neuromuscular block possibly by an ion-channel blocking action [6]. However, equivalent large doses were not used in this study. Other *in vitro* studies suggest that both cimetidine and ranitidine have anti-acetylcholinesterase properties, and this may explain why i.v. ranitidine antagonizes intense atracurium-induced neuromuscular block [4].

Drug interactions associated with cimetidine have been reported previously and it has been suggested that the mechanism of action was inhibition of the cytochrome P450 system, a reduction in liver blood flow, or both [1]. Because of its dependence upon hepatic function for metabolism, the breakdown of vecuronium may be reduced, resulting in the interaction observed. In contrast, atracurium, is not dependent on metabolism in the liver as it undergoes significant breakdown by spontaneous degradation at physiological temperature and pH. Observation of no differences between the groups in the time taken to onset of maximum block is not surprising, as this is related more to cardiovascular variables rather than to effects at the neuromuscular junction or factors such as hepatic blood flow.

In conclusion, we have shown that a single oral dose of cimetidine administered before operation prolonged the duration of action of vecuronium. This may not be important clinically where single relatively small doses of vecuronium are used, but may be important if patients are receiving chronic cimetidine therapy or if larger or repeated doses of vecuronium are administered.

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# TOTAL I.V. ANAESTHESIA WITH PROPOFOL AND ALFENTANIL FOR CORONARY ARTERY BYPASS GRAFTING

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**SUMMARY**

*The haemodynamic effects of total i.v. anaesthesia with a combination of propofol and alfentanil infusions were studied in eight patients with good left ventricular function undergoing coronary artery bypass surgery. Haemodynamic indices were measured before anaesthesia and at specified intervals before cardiopulmonary bypass. The technique resulted in haemodynamic changes comparable to those reported with opioid-based anaesthesia for coronary artery surgery, and has potential advantages.*

**KEY WORDS**

*Anaesthetics, intravenous: propofol Analgesics, opioid: alfentanil. Anaesthesia: cardiovascular.*

Induction of anaesthesia with propofol in patients with coronary artery disease results in significant reductions in mean arterial pressure, systemic vascular resistance and stroke volume [1]. A stepped manual infusion scheme was reported to attenuate the haemodynamic sequelae associated with induction of anaesthesia with propofol in patients without coronary artery disease [2]. We conducted a pilot study in patients undergoing coronary artery bypass grafting (CABG) and found an unacceptable incidence of arterial hypotension using the doses reported by Roberts and colleagues [2], but satisfactory anaesthesia and haemodynamic stability were achieved using 50 % the doses of propofol reported for the original stepped scheme [unpublished observations]. Russell and his colleagues [3] described the use of an infusion of propofol with intermittent doses of fentanyl in patients undergoing CABG, but the haemodynamic consequences of the combination of propofol and alfentanil infusions used for this purpose have not been reported. The latter combination produces satisfactory conditions for body surface surgery [4], and the pharmacokinetic profiles of propofol and alfentanil make both drugs suitable for continuous infusion for total i.v. anaesthesia. We have studied the haemodynamic effects of a combination of an alfentanil infusion together with a modification of the stepped manual infusion scheme described for propofol [2], for induction and maintenance of anaesthesia for CABG.

## METHODS AND RESULTS

Eight patients (seven male), mean (SD) age 60.3 (7.7) yr, weight 76 (11.8) kg, surface area 1.89 (0.21) $m^2$, scheduled to undergo CABG gave written consent to participate in the study, which was approved by the Hospital Ethics Committee. All patients had an ejection fraction greater than 0.5 and a left ventricular end-diastolic pressure less than 12 mm Hg. Maintenance doses of nitrates (seven patients), β-adrenoceptor antagonists (six patients) and calcium antagonists (seven patients) were continued until the morning of surgery. Lorazepam 0.06 mg $kg^{-1}$ was administered for premedication, 2 h before operation.

On arrival of the patient in the anaesthetic room, the ECG (lead II) was displayed continuously. Radial artery and pulmonary artery catheters and two peripheral venous cannulae were inserted using local anaesthesia. After 10 min the following baseline measurements were made: heart rate (HR), systolic (SAP), diastolic (DAP)

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and mean (MAP) systemic arterial pressures, systolic (SPAP) and diastolic (DPAP) pulmonary arterial pressures, right atrial pressure (CVP) and pulmonary artery wedge pressure (PAWP). Pressure measurements were made using calibrated transducers. Cardiac output was measured in triplicate by thermodilution (American Edwards Laboratories COM-1 computer). Cardiac index (CI), left ventricular stroke work index (LVSWI), systemic and pulmonary vascular resistance (SVR, PVR) were derived using standard formulae.

When the baseline measurements (A) were complete, 5 ml $kg^{-1}$ of modified gelatin solution (Gelofusine) and glycopyrronium 5 µg $kg^{-1}$ [5] were administered i.v. Anaesthesia was induced 5 min later with alfentanil 50 µg $kg^{-1}$ over 2 min, followed by a continuous infusion of 50 µg $kg^{-1}$ $h^{-1}$ and with propofol 0.5 mg $kg^{-1}$, followed by a stepped infusion of 5 mg $kg^{-1}$ $h^{-1}$ for 10 min, 4 mg $kg^{-1}$ $h^{-1}$ for a further 10 min and 3 mg $kg^{-1}$ $h^{-1}$ thereafter. Both drugs were administered via a dedicated peripheral venous cannula. Pancuronium 0.15 mg $kg^{-1}$ was used to provide neuromuscular block and the patient's lungs were ventilated mechanically to normocapnia with 100 % oxygen. The haemodynamic measurements were repeated 3 min after induction (B), 2 min after tracheal intubation (C), before skin incision (D), before (E) and after sternotomy (F). Glyceryl trinitrate 1–2 µg $kg^{-1}$ $min^{-1}$ was administered routinely to all patients when the measurements after sternotomy (F) were complete. Episodes of hypertension (an increase in SAP $> 20\%$ of preincision value) were treated with i.v. increments of alfentanil 25 µg $kg^{-1}$. The infusion rates of alfentanil and propofol were halved during hypothermic cardiopulmonary bypass and returned to their prebypass rate after the patients were rewarmed to 32 °C. All patients were questioned after operation about dreaming or recall of perioperative events. The haemodynamic variables at each time were compared with baseline values using ANOVA. The variables at time C were compared with those at B and the variables at F were compared with those at time E to assess the responses to intubation and sternotomy, respectively.

Induction of anaesthesia was associated with significant reductions in SAP (−22 %), MAP (−22 %), DAP (−18 %) and LVSWI (−30 %). No changes in ST segments were observed in any patient. There was no significant haemodynamic response to intubation and these variables returned gradually to baseline values after skin incision. There was no further haemodynamic response to sternotomy. Heart rate after tracheal intubation increased by a small but significant amount (+18 %) compared with baseline. There were no significant changes in pulmonary arterial pressures, CVP, PAWP, SVR and PVR (table I).

Three patients required three further increments of alfentanil after skin incision, and two patients received two increments after sternotomy. Six patients required vasoconstrictors (noradrenaline or phenylephrine) to maintain perfusion pressure greater than 50 mm Hg at the start of cardiopulmonary bypass (CPB); one patient received phentolamine to reduce a high perfusion pressure during CPB. No patient required inotropic support during weaning from CPB and none reported perioperative dreaming or recall of perioperative events. There were no new ischaemic changes on the postoperative ECG.

## COMMENT

The haemodynamic changes which we observed during induction were similar to those reported previously in patients with coronary artery disease receiving propofol [1], although the reductions in systemic arterial pressures observed were slightly smaller in our patients. This may reflect the lower doses of propofol used for both induction and maintenance of anaesthesia, and the pretreatment with glycopyrronium [5]. The technique provided good protection from the haemodynamic responses to intubation and sternotomy. Arterial pressures returned to baseline values with skin incision and sternotomy, but did not exceed the baseline value in any patient. Manual alteration of the infusion rates in anticipation of skin incision and sternotomy, or the addition of glyceryl trinitrate at the start of surgery, may further improve haemodynamic stability in the clinical situation when the anaesthetist is not restrained by a rigid research programme. These results compare favourably with the haemodynamic changes reported during opioid anaesthesia for CABG [6]. Large doses of opioid used as the sole anaesthetic for procedures with CPB result in haemodynamic stability, but opioids cannot be expected to produce unconsciousness reliably. Many anaesthetists therefore add volatile agents, but these may antagonize the desirable circulatory effects of large doses of opioids. The use of propofol and

TABLE I. *Haemodynamic data (mean (SD)) at times A–F associated with propofol and alfentanil infusions used for CABG. Significant differences compared with baseline*: $*P < 0.05$; $**P < 0.01$

| | A | B | C | D | E | F |
|---|---|---|---|---|---|---|
| HR | 63.3 | 69.9 | 72.8* | 69.5 | 69 5 | 68.1 |
| (beat $min^{-1}$) | (6.5) | (9.6) | (10.1) | (10.1) | (9.6) | (9.2) |
| SAP | 154.0 | 119.8** | 122.8** | 114.9** | 141.3 | 142.3 |
| (mm Hg) | (21.6) | (22.3) | (20.0) | (16.5) | (6 4) | (5.5) |
| DAP | 70.9 | 57.9* | 58.9* | 58.1* | 70.5 | 69.8 |
| (mm Hg) | (10.6) | (10.5) | (9.6) | (9.4) | (12.4) | (8.1) |
| MAP | 98.0 | 76.4** | 79.4* | 75.6** | 96.1 | 92.3 |
| (mm Hg) | (12.5) | (14.9) | (12.4) | (11.2) | (15.6) | (8.6) |
| SPAP | 21.3 | 23.1 | 24.5 | 18.4 | 21.1 | 20.5 |
| (mm Hg) | (4.4) | (6.9) | (7.6) | (4.4) | (4.5) | (3.4) |
| DPAP | 6.8 | 8.5 | 8.8 | 8.0 | 10.6* | 8.4 |
| (mm Hg) | (2.3) | (2.4) | (3.3) | (2.7) | (2.4) | (1.8) |
| CVP | 3.0 | 4.0 | 2.8 | 3.8 | 5.0 | 5.0 |
| (mm Hg) | (2.7) | (2.1) | (1.9) | (1.4) | (1.3) | (2.0) |
| PAWP | 3.6 | 4.9 | 5.1 | 3.5 | 6.9* | 5.6 |
| (mm Hg) | (2.4) | (2.0) | (1.7) | (1.4) | (2.9) | (1.4) |
| CI | 4.3 | 4.2 | 4.5 | 3.6 | 3.8 | 3.7 |
| (litre $min^{-1}$ $m^{-2}$) | (0.9) | (0.7) | (0.8) | (0.8) | (0.8) | (0.9) |
| SVR | 1011.0 | 757.0 | 751.0 | 905.0 | 1068.0 | 1067.0 |
| (dyn s $cm^{-5}$) | (408.0) | (247.0) | (230.0) | (284.0) | (326.0) | (286.0) |
| PVR | 98.0 | 99.0 | 93.0 | 102.0 | 85.0 | 90.0 |
| (dyn s $cm^{-5}$) | (38.0) | (34.0) | (29.0) | (27.0) | (19.0) | (27.0) |
| LVSWI | 87.0 | 60.9* | 63.6* | 51.0** | 69.5 | 67.0 |
| (g m $m^{-2}$ $beat^{-1}$) | (23.5) | (17.5) | (18.8) | (12.2) | (18.1) | (18.4) |

alfentanil infusions allows separate control of the anaesthetic and analgesic components without the haemodynamic consequences of adding volatile agents, and without the need for large doses of opioids which may result in a prolonged requirement for ventilatory support after operation.

Propofol and alfentanil infusions offer stable and pollution-free anaesthesia for CABG in patients with good left ventricular function. Further studies are required to assess if the theoretical advantages of this technique may be realized in cardiac anaesthetic practice.

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# INTRA-ARTERIAL REGIONAL ANALGESIA OF THE HAND

## Z. J. KOSCIELNIAK-NIELSEN AND H. L. STENS-PEDERSEN

### SUMMARY

*Fifteen millilitre of 0.5% lignocaine was injected into the radial artery to provide analgesia for hand surgery in an elderly arthritic female patient. She experienced only minimal discomfort during injection and analgesia was excellent. No untoward effects were observed. This technique is recommended when other methods of regional analgesia are unavailable.*

***KEY WORDS***

*Anaesthetic techniques intra-arterial regional.*

Intra-arterial regional analgesia is almost obsolete today, as other, safer methods are available. However, it may be valuable in specific patients, when regional analgesia of rapid onset is required and other techniques have a greater risk. A case is reported and the method discussed.

### CASE REPORT

A 66-yr-old woman, slight and frail (154 cm, 44 kg) was scheduled for elective arthrodesis of the proximal interphalangeal joint of the left thumb. She was crippled severely by rheumatoid arthritis, and had a long history of asthma. Daily medication was prednisone, piroxicam and salbutamol.

Before operation she was noted to have almost unusable hands, significant kyphosis of the thoracic spine, a very stiff neck and limited mouth opening. Shoulder joints were affected also, limiting abduction of both arms to about 60–70°. Her skin was pale and thin, almost parchment-like, with very fragile, tortuous veins. She was mentally remarkably lucid, but slightly depressed by chronic disease and invalidity.

After we had reviewed the risks of general anaesthesia, the patient agreed to i.v. regional analgesia (IVRA), and was premedicated with diazepam 10 mg orally.

In the operating theatre a 20-gauge i.v. catheter was placed at the second attempt in the unoperated hand. Three unsuccessful attempts were made to cannulate a vein in the affected hand, first by a nurse anaesthetist and then a registrar. Further help was enlisted as both patient and personnel were becoming visibly distressed. Intra-arterial (i.a.) regional analgesia was then proposed. The procedure was explained to the patient and accepted.

The radial artery was cannulated with a 22-gauge Teflon catheter. After the upper arm tourniquet was inflated to 100 mm Hg greater than the systolic arterial pressure, 0.5% lignocaine 15 ml without vasoconstrictor was injected i.a. over about 30 s. At the start of injection the patient experienced a burning sensation which soon ceased. Within 30 s the forearm and hand became uniformly pale, with only a minimal marble appearance. Sensation to pinch was lost within 3 min. The arterial catheter was removed and compression applied for another 3 min, after which surgery was allowed to proceed.

Anaesthesia and surgery were uneventful and both patient and surgeon were satisfied. Analgesia of the hand was excellent, gradually disappearing over 3–4 min after release of the tourniquet. During the procedure the patient received fentanyl 0.1 mg and Diazemuls 5 mg i.v. to ease the discomfort of being immobile on the operating table.

### DISCUSSION

Intra-arterial regional analgesia was described first by Goyanes in Spain in 1912 [1]. Later it fell into disuse, despite a brief revival by Van Niekerk

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and Coetzee in the mid 1960s [2]. It is described briefly by Atkinson, Rushmann and Lee in *A Synopsis of Anaesthesia* [3].

In our patient it was probably the only remaining technique to provide good analgesia for the hand surgery without resorting to general anaesthesia. Having considered the risks of general anaesthesia, the patient was not willing to accept them. Alternative techniques were considered and rejected for the following reasons: Axillary block would have been difficult, as arm abduction was limited, the axillary artery barely palpable and the patient upset by previous attempts at catheterization. Higher approaches to the brachial plexus were impossible because both shoulders were elevated by arthritis and could not be depressed enough to make room for palpating fingers. A blind search for the plexus was considered too risky in a patient with asthma, emphysema and fragile blood vessels. As an arm tourniquet was to be used to provide a "bloodless field", nerve blocks at the elbow were felt to be unsuitable. No other vein could be found in the cubital fossa. Infiltration analgesia could not be performed satisfactorily.

Two possibilities remained, neither of which had been attempted by us before. Transverse injection anaesthesia (so called "squirt and cut or Vishnevsky technique" [4]) was used for amputations during the Crimean war, but was inapplicable in our patient as injections had to be made at the tourniquet level; considerable pain would result from the multiple injections, and toxic effects of large volumes of local analgesic would be likely. The second choice was i.a. regional analgesia, which seemed to be the most appropriate. It was decided to inject the analgesic into the radial artery, as in older patients with stiff arteries, injection into the brachial artery may carry the risk of leakage under the cuff, with insufficient analgesia in the hand. Lignocaine 0.5 % was used as it is a standard drug for i.v. local analgesia at our hospital.

Rapid onset of the block may be explained by perfusion of capillary beds rather than back diffusion as in IVRA. The only complication noted was a haematoma at the site of radial artery puncture, which could probably have been prevented by maintaining compression for longer.

The total dose of lignocaine injected i.a. was 75 mg, which is the maximum recommended by Van Niekerk and Coetzee [2].

Intra-arterial local analgesia is a useful alternative for analgesia of the arm when other techniques are impractical or impossible.

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# INTRAOPERATIVE DEATH DURING LUMBAR DISCECTOMY

## B. EWAH AND I. CALDER

***SUMMARY***

*A patient suffered cardiovascular collapse and died during surgery for prolapsed intervertebral disc. At postmortem a tear was found in the abdominal aorta.*

***KEY WORDS***

*Surgery: neurological. Complications: death, perforated aorta.*

### CASE REPORT

A 26-yr-old woman was referred for surgical treatment of a prolapsed lumbar intervertebral disc at L4–5, diagnosed by myelography. Her symptoms of unilateral leg pain with a mild L5 radiculopathy had failed to settle with 1 month bed rest at another hospital. She had otherwise good health and did not smoke, but was moderately obese and was receiving the contraceptive pill.

Premedication comprised papaveretum 15 mg and hyoscine 0.3 mg. Anaesthesia was induced with thiopentone followed by atracurium. The trachea was intubated and anaesthesia maintained with 1% isoflurane and 66% nitrous oxide in oxygen. Atracurium was infused at a rate of 20 mg $h^{-1}$. A 14-gauge i.v. cannula was inserted in a forearm vein and a crystalloid infusion commenced. Monitoring included ECG, $Sp_{O_2}$ (Datex Satlite), end-tidal carbon dioxide concentration (Hewlett-Packard 47210A) and non-invasive measurement of arterial pressure (Accutor Datascope 1A). Arterial pressure was measured and printed at 5-min intervals. The patient was placed prone, the tissues incised and the appropriate disc space identified by counting spines upwards from the sacrum. The disc appeared abnormal, in that the annulus was bulging, and a routine discectomy was performed with pituitary rongeurs. The surgeon had not noticed anything unusual during discectomy, but felt that a radiograph should be obtained to check that the correct level had been operated upon. Whilst this was being obtained some 5 min after the discectomy, the monito alarms began almost simultaneously. $Sp_{O_2}$, end tidal carbon dioxide, heart rate and arterial pressure readings had been stable for the preceding 1 h. The oximeter alarm activated first flashing "low quality signal" and providing no reading. This was followed almost immediately by the capnograph, which flashed a calibration code signal and absence of end-tidal carbon dioxide. The Accutor failed to record arterial pressure and flashed "no pulsation detected". The ECG complexes were normal, but the hear rate had increased from 90 to 110 beat $min^{-1}$. There was no bleeding from the wound and the carotid pulse was not palpable.

The patient was turned supine, and ventilation continued with 100% oxygen. Her chest was auscultated and both heart and breath sounds were normal. External cardiac massage was commenced. Haemaccel 1 litre was infused rapidly and ephedrine, adrenaline and calcium chloride were given. No femoral pulse was palpable bu needling produced pink blood, analysis of which showed pH 7.135, $P\text{CO}_2$ 2.9 kPa, $P\text{O}_2$ 66.7 kPa, $\text{HCO}_3$ 7.6 mmol $\text{litre}^{-1}$, base excess −22 mmo $\text{litre}^{-1}$ and oxygen saturation 99%. Internal jugular vein cannulation was unsuccessful. The groin was incised and the femoral artery and vein cannulated. The artery was collapsed and no blood emerged from the cannula, whilst the vein was distended. The patient's abdomen was soft and did not seem distended. Resuscitation was continued with i.v. crystalloid, colloid and ino-

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tropes. $Sp_{O_2}$ values in the range 70–79% were obtained, with end-tidal partial pressure of carbon dioxide in the range 1.3–2.6 kPa. A carotid pulse was palpable briefly, but after 40 min the ECG complexes became abnormal and cardiac arrest occurred.

At postmortem examination it was found that the L3–4 disc had been removed and that there was a 0.5-cm laceration in the aorta at that level. The retroperitoneal space was full of blood, which had also passed into the peritoneal cavity.

## DISCUSSION

Our patient presented with electromechanical dissociation (EMD). The causes of EMD include pulmonary embolism, severe hypovolaemia, myocardial infarction, cardiac tamponade and pneumothorax. Our initial diagnosis of pulmonary embolism was not supported by the results of blood-gas analysis. We considered the possibility of aortic damage, but did not make the correct diagnosis because: there was no bleeding from the wound; the surgeon did not believe he had perforated the anterior longitudinal ligament (ALL); circulatory collapse was sudden and severe; the abdomen appeared soft and not distended; surgery was being performed at L4–5, below the bifurcation of the aorta.

A review of the literature showed that bleeding from the wound has been seen from fewer than 50% of reported cases of vascular damage [1]. This is perhaps not surprising. Both the ALL and disc annulus are tough, elastic structures and thus effectively self-sealing. Blood leakage from the aorta or inferior vena cava (IVC) would be expected to take the line of least resistance into the retroperitoneal space. The literature suggests that surgeons are often unaware that they have perforated the ALL [1, 2], but reports emphasize the ease with which perforation can occur [3] because of the anatomical proximity of the lumbar disc space to the great vessels.

Circulatory collapse may be sudden and may be confused with cardiac arrest [3, 4]. It is conceivable that an expanding retroperitoneal haematoma might occlude the IVC, which would contribute to circulatory collapse. In our patient, the femoral vein was certainly distended. However, haemorrhage from a lacerated aorta is likely to be severe enough to produce "sudden" collapse unless the arterial pressure is recorded continuously. A continuous recording of arterial pressure from an arterial catheter would have been helpful during resuscitation attempts, but we doubt if it would have affected the outcome. In view of the rarity of vascular damage during discectomy (see below), we doubt if invasive monitoring is justified.

The patient's abdomen must have become distended, but we did not recognize it, perhaps because of her obesity. Telephone consultation with a cardiovascular surgeon took place during the resuscitation: the lack of abdominal swelling and absence of bleeding from the wound was remarked upon and a diagnosis of aortic dissection suggested. Aortography was considered, but after discussion with a consultant radiologist we felt that it would be of little help, given the collapsed state of our patient.

It is not uncommon for surgeons to operate at a level different to that intended. It is surprisingly difficult to identify a particular intervertebral joint and if the disc appears abnormal, as it did in our patient, it is likely to be removed. Although the aorta usually bifurcates before L4–5, severe haemorrhage may occur from lacerated iliac vessels after perforation at this level. The possibility that the surgery has been performed at a level different from that intended must always be considered.

Vascular damage during discectomy is rare: Gurdjian and colleagues suggested an incidence of 5 cases in 10000 discectomies [5]. Mortality is high after aortic perforation (78%) and greater after IVC perforation (89%), but considerably less after iliac vessel damage [1]. Perforation of the small and large bowel has occurred also [6]. Aortic damage was reported first in the U.S.A. in 1948 by Falconer, McGeorge and Begg [7], but a case has not been reported previously in the United Kingdom.

Mortality after perforation of the aorta is 100% unless rapid diagnosis, laparotomy and control of haemorrhage are achieved. Diagnosis rests largely on a knowledge of the condition. In particular, it must be appreciated that overt bleeding from the wound is not seen in the majority of cases. Any sudden collapse around the time of discectomy should be assumed to be caused by concealed haemorrhage until proved otherwise. Angiography or CT scanning may be helpful in less acute presentations [8, 9].

Laparotomy, exposure and possibly clamping of the aorta may be within the competence of most surgeons, but repair of the laceration is likely to be difficult, especially if it is on the dorsal aspect of the aorta. Transluminal repair, transection, patching or grafting of the aorta may be necessary. Expert vascular surgical assistance will be required.

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# DIAGNOSTIC AND MANAGEMENT DILEMMAS IN A PATIENT WITH TRACHEAL TRAUMA

## J. K. BRIERLEY, J. OATES AND D. G. BOGOD

**SUMMARY**

*A patient with a foreign body penetrating the neck and chest was found to have physical signs which were consistent with serious tracheal injury and included a large movement of air through the lower part of the neck. The subsequent management of the patient and the difficult problem of securing an airway are described. At operation, the tracheal damage was found to be less severe than anticipated and the observed air flow was a result of penetration of the foreign body into the pleural cavity. The management of the patient is discussed and the potential for misinterpretation of the physical signs in this type of trauma is emphasized.*

**KEY WORDS**

*Airway trauma. Intubation, tracheal: fibreoptic.*

The immediate management of penetrating injuries to the airway is an uncommon, but difficult challenge for the anaesthetist and the surgical team [1]. This report describes the presentation and subsequent management, in the accident and emergency department, of a patient who had suffered trauma to the chest and trachea.

### CASE REPORT

The patient was a 26-yr-old lorry driver, whose vehicle had been in collision with a caravan. He had become impaled on a large piece of the distorted aluminium frame from the rear window of the caravan, which penetrated his neck in the midline anteriorly immediately above the suprasternal notch and passed downwards and laterally into the left side of the chest. He had remained trapped in his cab for 1 h before being cut free and transferred to the accident and emergency department.

When seen first in hospital, the patient was sitting upright, with the foreign body clearly visible, emerging from a large wound above the sternum (fig. 1). He was alert and pale but with a stable cardiovascular system and, although tachypnoeic, was not cyanosed or showing signs of ventilatory obstruction. He was complaining of pain in the left lower chest posteriorly, and had poor air entry in this zone. The arterial $P_{O_2}$ with the patient breathing air was 9.6 kPa. A pneumothorax was suspected, so a chest radiogram was obtained from a portable machine, and this showed a left haemopneumothorax which was drained immediately. Because a large airflow was noted round the point of entry of the metal, an oxygen mask was adapted and positioned over that area, on the assumption that the foreign body

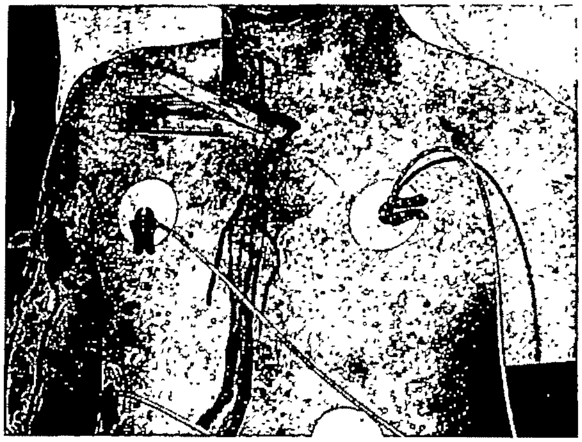

FIG. 1. The patient on arrival in the Accident and Emergency Department.

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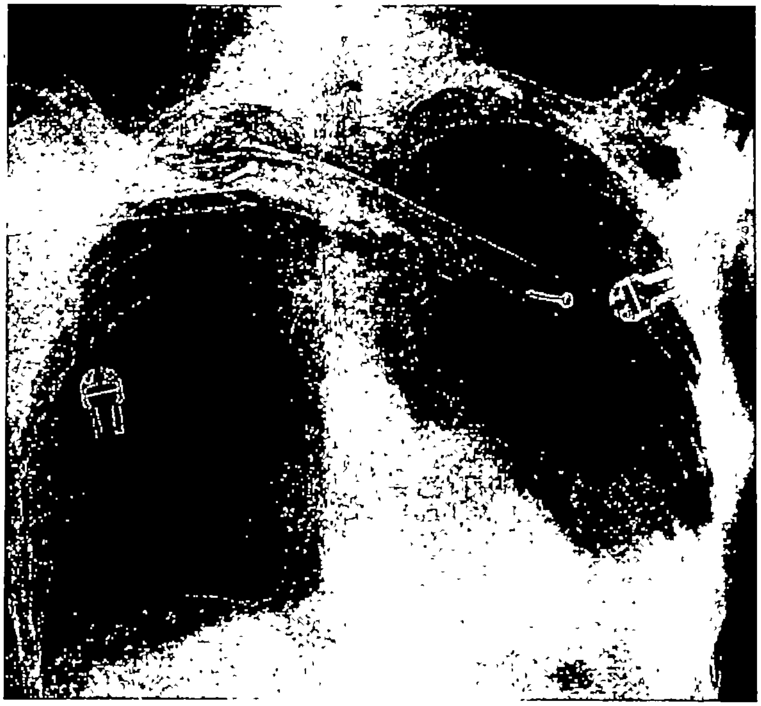

FIG. 2. Chest radiograph taken on arrival at hospital. The arrows indicate the edge of the collapsed left lung

had caused a large breach in the trachea. This appeared to be confirmed both by the chest x-ray (fig. 2) and by the fact that when the patient attempted to talk he could produce only a very weak, whispered noise. The exact location of the metal strip was difficult to assess from the chest x-ray, but it crossed the line of the trachea about 4 cm above the carina and entered the left side of the chest above the arch of the aorta. The strip was 3 cm wide, 34 cm long and 1.5 cm deep, with silastic sealant and windscreen glass embedded in the posterior surface and 2.5-cm screws projecting laterally in two places (fig. 3).

A vein was cannulated, blood crossmatched and the patient transferred to the operating theatre, where fibreoptic bronchoscopy was performed under local anaesthesia. This revealed a normal upper airway, but an immobile left vocal cord. Surprisingly, the lumen of the trachea was completely patent, with the edge of the metal strip visible through a small tear in the tracheal wall. Tracheal intubation was achieved by feeding a 7.0-mm i.d. cuffed, armoured tube over the bronchoscope and positioning the tube tip under direct vision, below the area of tracheal damage but above the carina. With the airway secured in this manner, a general anaesthetic was administered and intermittent positive pressure ventilation commenced. The anaesthetic proceeded in an uneventful manner.

At operation, median sternotomy was performed and the foreign body was found to be lying in contact with the trachea, which had two small cuts in the left side. It had then passed from the midline, between the left subclavian and left common carotid arteries, touching both vessels and the arch of the aorta. Following this it had travelled over the apex of the left lung and become embedded through the posterior chest wall into the scapula. A small area of lung contusion was noted. The recurrent laryngeal nerve and the thoracic duct had been severed on the left, but there was remarkably little additional damage. It was necessary to remove the distal screw before the strip could be withdrawn through the great vessels, the trachea repaired and the left lung re-expanded. The patient was sent to the Intensive Care Unit where the trachea was extubated 36 h later. His recovery was rapid, marred only by the presence of a persistent left pneumothorax, pre-

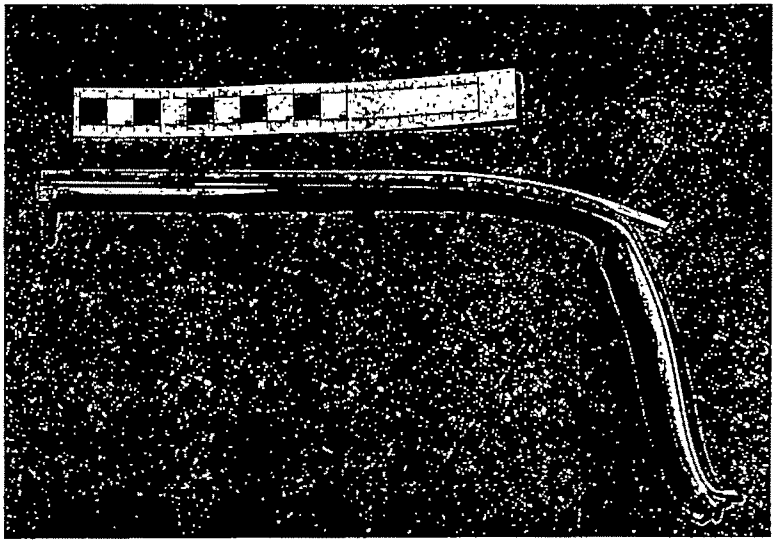

FIG. 3. The metal strip after its removal. The measure is marked in cm.

sumed to be caused by a small air leak from the area of the damaged lung.

## DISCUSSION

There are several points which merit discussion in the management of this difficult case. At the time he was first seen in the accident and emergency department, the patient was in a stable condition, but with an injury the full extent of which was unknown. The physical signs and the chest x-ray suggested that the trachea was transfixed by the metal strip a short distance above the carina and our approach to this patient, therefore, was dictated by the erroneous assumption that, because of the considerable air movement in and out of the neck wound, there was significant tracheal disruption. The lateral chest radiograph failed to provide evidence regarding the precise position of the foreign body. Clearly, it was necessary to explore the chest before the metal could be removed, as the presence of the screw would make further damage unavoidable if the strip was simply withdrawn. The foreign body emerging from the neck also made it impossible to reach the trachea through the neck opening. However, the prospect of general anaesthesia was untenable without some method of securing an airway. The maintenance of full power and control in the neck and pharyngeal musculature is of prime importance in the support of a disrupted trachea, and the inevitable loss of this power associated with general anaesthesia could have resulted in airflow obstruction. With severe damage to the trachea, a blind attempt at tracheal intubation could have had disastrous effects on the patency of the airway, as could the use of positive pressure ventilation. The possibility of establishing cardiopulmonary bypass by the femoral route under local anaesthesia was not a viable option, as there was no facility available for this procedure locally. The patient was unfit to travel and transfer of personnel and equipment to this centre would have delayed treatment for too long. Dissection of the area under local anaesthesia, insertion of a catheter into the right main bronchus and insufflation of the right lung was considered, but dismissed, because access to the distal trachea was prevented by the foreign body lying hard against the suprasternal notch. In addition, its further movement might have caused damage to the great vessels. An alternative approach, equally valuable for the intact and the disrupted trachea, would have involved the use of high frequency jet ventilation via a tracheal tube passed into the upper larynx but, in the event, our use of the fibreoptic bronchoscope revealed a patent airway and resolved our dilemma.

It transpired that the damage to the trachea was far less serious than we suspected initially as a result of misinterpretation of the physical signs. In view of our extreme concern about the patient's condition and the urgent need to transfer him to theatre, we did not repeat chest radiography after insertion of the chest drain. Had we done so, it would have shown us that the left lung had not re-expanded although the haemothorax had drained. The movement of air which we observed through the front of the neck around the metal strip was merely transfer of air in and out of the left pleural cavity. Indeed, it is worth noting that any attempt by ambulance personnel at the accident scene to cover the neck wound may have produced a tension pneumothorax. The tear in the trachea was small and the major proportion of the respiratory gases was still passing through the upper respiratory tract. We ascribed the poor phonation primarily to a lack of air passing through the larynx rather than to the combination of a severed recurrent laryngeal nerve and a reluctance to speak with a painful chest injury.

There are lessons to be learned from this case; there may be more than one plausible explanation for a combination of physical signs seen with a penetrating neck and thoracic injury and it cannot be assumed that the first diagnosis which springs to mind is the correct one, however perfectly it fits the circumstances. Therefore, despite the great pressure to move the patient rapidly towards the definitive treatment [2], there must be continued observation for new developments and further investigations should continue if circumstances permit. In this patient, the simple expedient of using a facemask and Water's bag to look for movement of air through the upper respiratory tract would have been a useful guide to the extent of the injury before more invasive procedures were embarked upon. It must be borne in mind, however, that even with convincing proof of airflow through the larynx, the possibility of tracheal transection could not be excluded [1]. In addition, evidence from a further examination of the chest, viewed in conjunction with the lack of bubbling from the chest drain and a repeat chest x-ray could have given valuable clues. The clinical and radiological presence of mediastinal and subcutaneous emphysema, in addition to a continued air leak after the insertion of the chest drain, would have strongly suggested tracheal disruption. However, our patient was managed safely and successfully despite the diagnostic difficulties.

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# POSTERIOR SPINAL FUSION IN SOTOS' SYNDROME

D. SURESH

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**SUMMARY**

*Sotos' syndrome (synonym: cerebral gigantism) is the association of mental retardation, macrocephaly and prenatal onset of accelerated growth. The rapid skeletal growth may account for a 4% incidence of scoliosis. General anaesthesia using halothane or enflurane in nitrous oxide and oxygen, with opioid supplementation and labetalol to induce moderate hypotension, appeared to be a satisfactory technique for corrective spinal surgery. The potential problems are discussed, with mental retardation and sometimes aggressive behaviour contraindicating a "wake-up" test. Extradural somatosensory evoked potential monitoring is a satisfactory alternative. Hook failures seem more likely than in patients undergoing surgery for adolescent idiopathic scoliosis.*

**KEY WORDS**

*Anaesthesia: general Complications. Sotos' syndrome. Surgery: spinal fusion.*

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Sotos' syndrome (synonym: cerebral gigantism) is the association of mental retardation, macrocephaly and prenatal onset of accelerated growth inherited as an autosomal dominant trait [1]. Bone age is advanced in all children, and although scoliosis is not part of the syndrome complex, rapid skeletal growth may account for a 4% incidence as reported in one series [2]. Patients may therefore present for surgical correction of their scoliosis.

## CASE REPORT

A male child was delivered by forceps at 42 weeks following an uncomplicated pregnancy; he weighed 4.2 kg at birth. He suffered from "jerks" which ceased at age 1 yr, and his early motor, speech and language development was reported also to be delayed.

There was no family history of Sotos' syndrome. Manifest features included growth pattern, hypertelorism and palpebral fissures, prognathism, receding hairline and large spadelike hands with a single palmar crease on the right. Pubertal development was nearly complete, with small external genitalia and scanty pubic hair, but no pigmentation [3]. He had a clumsy gait, and showed psychomotor retardation. He could be difficult and stubborn and only his parents were able to influence his behaviour, although intellectually he was not as impaired as he appeared.

The main musculo–skeletal features were accelerated linear growth and skeletal maturation. Kyphoscoliosis was obvious from the age of 4 yr, with some pelvic instability. When he was 11 yr, a right thoracic scoliosis was treated with a brace for 8 months. An x-ray examination in and out of the brace showed a 48° right thoracic curve at the T4–10 level, and a 52° left lumbar curve between T11 and L4. When he was admitted for correction of his scoliosis, this had deteriorated to a 70° right and a 70° left lumbar scoliosis, represting a 20° deterioration over the previous 10 months.

At the age of 14 yr, the subject weighed 90 kg, his height was 170 cm and his arm span measured 178 cm. Cardiovascular and neurological assessment were unremarkable. Lung function tests revealed a restrictive defect with a forced vital capacity (FVC) of 1.7 litre (32% of predicted norm). A glucose tolerance test and anterior pituitary functions were normal and a lateral radiograph of the skull showed a normal pituitary fossa. Routine haematology and biochemistry screens were within normal limits, as were serum concentrations of 17-OH progesterone, calcium, phosphate and alkaline phosphatase. He snored

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and had been investigated recently for sleep apnoea, the results of which were reported as negative. There were recent behavioural problems and his behavioural age was estimated to be about 6 yr.

### *Anaesthesia*

Because the patient hated needles, premedication consisted of diazepam 10 mg orally. Both parents were present during induction of anaesthesia, which would have been impossible without their calming influence. The facemask was held by the father for induction of sleep with halothane in oxygen. Vecuronium 10 mg was given to facilitate intubation with a 9.0-mm cuffed orotracheal tube, with additional intermittent doses to facilitate IPPV. Anaesthesia was maintained with 1–2% halothane and 65% nitrous oxide in oxygen. A radial artery cannula and a right internal jugular cannula were inserted. The patient was placed prone on a Montreal mattress and the extradural space at C7–T1 was located using the "hanging drop" technique with a 16-gauge Tuohy needle [4]. A 3-French gauge bipolar recording electrode was positioned in the extradural space and connected to a Medelec MS 91 electomyograph recorder. The right and left posterior tibial nerves were stimulated alternately via skin surface electrodes using a square wave impulse of 0.2 ms duration at an intensity of 150 µV. The stimulation frequency was 20 $s^{-1}$ and 1000 responses were averaged with a resolution of 0.33 ms and with the filters set at 200 Hz to 2 KHz.

Intermittent doses of pethidine were given to supplement anaesthesia, and hypotension to systolic pressures of about 70 mm Hg was achieved with labetalol (total 85 mg). As the quality of traces from the spinal cord monitoring was poor, a distal electrode was inserted at L1–2 and this provided good traces between this and the stimulating electrode, but not superiorly. An additional electrode was sited therefore at the T3–4 interspace; this resulted eventually in satisfactory recordings from the posterior tibial nerves. The operative procedure consisted of internal fixation of a contoured Harrington rod, stabilized at each level with Luque sublaminal wiring. Intraoperative fluid replacement included crystalloid 1000 ml, colloid 2000 ml and 3 units of plasma reduced blood.

The procedure, including customizing a subortholene plaster cast prescribed for the next 8 months, lasted 6 h 15 min. The patient was awake a few minutes after antagonism of neuromuscular block, when clinical testing allowed confirmation of intact neurological function as indicated by the continuous intraoperative somatosensory evoked potential (SEP) monitoring.

### *Postoperative course*

There was a slight ooze from the wound and perioperative blood loss totalled 3250 ml. There was a short episode of unexplained supraventricular tachycardia which settled later to about 120 beat $min^{-1}$. An infusion of papaveretum 4 mg $h^{-1}$ provided satisfactory analgesia. He received assisted positive pressure ventilation with a Bird ventilator according to a standard procedure —initially hourly until his FVC was 25% of best preoperative value, then 2 hourly until FVC was 50%, and thereafter 4 hourly until 75% of the baseline values had been attained [5].

The boy made satisfactory progress until 2 weeks later, when an erect radiograph of the spine revealed that the top hook at T4 had cut out and approximately 20° correction had been lost. He was prepared for surgery on the following day. This time there was less objection to both i.m. premedication and i.v. induction with thiopentone. The trachea was intubated using suxamethonium and IPPV was facilitated by a single bolus of vecuronium 5 mg. Anaesthesia was maintained with enflurane and nitrous oxide in oxygen and intermittent doses of papaveretum provided analgesia. Labetalol (total 40 mg) was used again for hypotension to systolic values similar to those in the first operation. SEP monitoring was uncomplicated and re-fixation of the upper rod was completed uneventfully and with minimal blood loss. A urinary catheter was not inserted on this occasion. As before, tachycardia (140 beat $min^{-1}$) and a transient pyrexia of 39 °C were noted on the first day after operation.

Six days later, several episodes of frank painless haematuria occurred, the cause for which remained unexplained despite exhaustive investigations. This settled as spontaneously as it began and allowed discharge from hospital the following week.

When reviewed 1 month later, radiography revealed that the lower hook at T12 had dislodged. Fortunately, the multilevel sublaminal wire fixation reinforced by the plaster cast maintained a reasonable correction for the thoracic curve and the patient was advised to remain in plaster for 8 months.

## DISCUSSION

Scoliosis is often a part of various malformation syndromes, and with the added factor of accelerated skeletal growth, an incidence of 4% is not unexpected in the Sotos' syndrome [2]. Metacarpophalangeal analysis aids diagnosis [6] and although the syndrome is inherited as an autosomal dominant disorder, a recessive pattern of inheritance has also been suggested [7].

Excessive head growth in early infancy is a typical feature [8], and hydrocephalus with increased intracranial pressure has been reported [9]. Craniofacial features at variance with the characteristic description include acrocephaly and maxillary prominence. Steepness of the anterior cranial base and protrusion of the middle and lower face shown by cephalometric radiographs [10], with potential for difficulty with the airway, also have been reported. Increased somatomedin activity and increased secretion of growth hormone have been observed [9], and it is essential to exclude glucose intolerance. Other features of possible relevance to anaesthesia include lipid storage myopathy [11], hypotonia and clumsiness [12], high arched palate complex [13] and cardiac abnormalities [14].

High rates of emotional and behavioural disorders are common, and all children in one study presented with cognitive impairment or mental retardation [15], which may be associated with hyperactive and aggressive behaviour [7]. This presents problems of peroperative co-operation, especially with regard to the wake-up test. Continuous SEP monitoring is therefore prudent if not mandatory in these patients, as disappearance of one of the triple peaks characteristic of the extradural SEP trace or a decrease in overall amplitude by 50% would indicate immediately a need for modification of the surgical manoeuvre. Neither of these events was noted during the initial or subsequent surgical procedure in this patient (fig. 1).

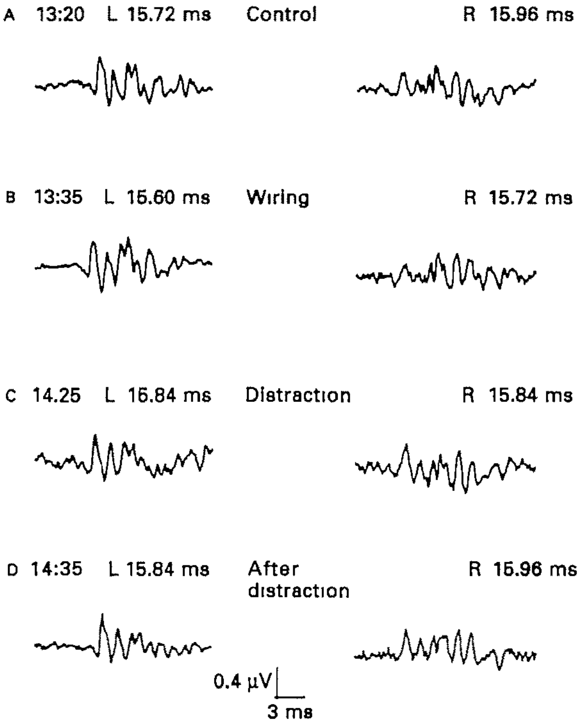

FIG. 1. Sample extradural SEP recordings in response to alternate right and left posterior tibial nerve stimulation from electrode sited at C7–T1. A = control; B = during sublaminal wiring; C = during distraction; D = 10 min after distraction. Baseline latency: L = 15.48 ms, R = 15.72 ms; baseline amplitude: L = 0.6 µV and R ≐ 0.2 µV.

Apart from minor variations, the anaesthetic management of this patient conformed to that used at the Royal National Orthopaedic Hospital, for posterior spinal fusions in adolescent idiopathic scoliosis (AIS) [5]. Induced hypotension is used routinely in scoliosis surgery and is associated with significantly less peroperative mean blood loss [16]. Enflurane and opioid supplementation are of additional benefit by reducing operating time, blood loss and the need for blood replacement [17]. It has been suggested that it is possible to eliminate completely the requirement for transfusion in routine posterior spinal surgery, if meticulous surgical and anaesthetic techniques are combined with autotransfusion [18].

No complication of induced hypotension has been recorded in this institution and a reduction in mean arterial pressure to 62 mm Hg during anaesthesia for AIS resulted in only a 25% change in mean overall amplitude of SEP [5, 19]. A possible additive effect of hypotension on the SEP during spinal distraction should be considered, as this has been shown to occur in the feline spinal cord compression model [20]; however, there is no study which has quantified or compared this with the individual effects of induced hypotension and spinal distraction on the

SEP during scoliosis surgery. This information would be of value in balancing the risks and consequences of excessive blood loss and transfusion against the degree of correction achievable without risk to the spinal cord.

In a study of the effects of halothane, enflurane and isoflurane on SEP during nitrous oxide based anaesthesia, it was found that enflurane and isoflurane resulted in less alteration of somatosensory cortical evoked potential than halothane [21]. This finding may have been a consequence of a pronounced effect of inhalation agents on SEP recorded cortically [22], as it has been demonstrated that extradural SEP are affected minimally by halothane in an end-tidal concentration of 1.5% [19]. SEP recordings for the two operations in this patient confirm an additional advantage of the extradural technique—that of reproducibility.

The incidence of hook failures following posterior spinal fusion in AIS is 2.5% in this centre and may be related to deep wound infection. The top hook is found to dislodge more frequently (63%) than the bottom hook (37%). In a review of 319 patients over a period of 8 yr, not one case of double hook failure was noted, suggesting that such a complication may be peculiar to this syndrome [5].

Trauma to bone and muscle, blood loss and hypotensive anaesthesia might be reasonably expected to compromise renal function, but a prospective study of 43 patients undergoing a total of 52 operations for scoliosis correction failed to reveal any evidence of renal impairment [23]. The haematuria following the second operation in our patient was therefore worrying, but ceased spontaneously and remained unexplained despite exhaustive investigation and consideration of rarer causes such as adverse reaction to cephalosporins, known to interfere with clotting.

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*British Journal of Anaesthesia* 1991; **66**: 733–735

# CORRESPONDENCE

## RAPID ONSET OF SUXAMETHONIUM BLOCK

Sir,—Suxamethonium is used widely for "crash" induction of anaesthesia because of its rapid onset of action. In contrast, non-depolarizing neuromuscular blocking drugs have a relatively slow onset.

The present report supports the hypothesis of Feldman, Fauvel and Harrop-Griffiths, who postulated that the rapid onset of suxamethonium block may be secondary to its depolarizing nature [1]. Pretreatment with a non-depolarizing agent such as vecuronium may change the nature of suxamethonium block, and slow its onset.

In five adult patients, anaesthesia was induced with ketamine 2 mg $kg^{-1}$. Suxamethonium 100 mg produced complete neuromuscular block after 60–90 s, and showed 75% recovery in 5–10 min. The block was depolarizing in nature, as indicated by a T4:T1 ratio $> 0.85$. When the same dose of suxamethonium was injected after establishment of a 25–50% block by vecuronium, complete block was achieved after 120–180 s, and 75% recovery occurred after 3–5 min; the block showed a T4:T1 ratio $< 0.3$ (fig. 1).

The results suggest that vecuronium may not only compete with suxamethonium for the endplate cholinergic receptors, but may also change the nature of its block from pure depolarizing into mixed or even non-depolarizing. This may explain the slow onset of block observed when suxamethonium was administered after vecuronium.

The concept of the margin of safety of neuromuscular transmission [2] may explain the different onsets of depolarizing compared with non-depolarizing block. Waud and Waud demonstrated that the twitch response is not reduced unless more than 70% of receptors are occupied by a non-depolarizing neuromuscular block, and the twitch is eliminated completely when 90% of receptors are occupied [3]. It is possible, therefore, that suxamethonium can produce depolarizing neuromuscular block when only 10–30% of endplate receptors are occupied.

Our results suggest that the difference in onset times between depolarizing and non-depolarizing blockers may be attributed to the different proportions of endplate receptors that need to be occupied in order to achieve neuromuscular block. Thus the rapid onset of suxamethonium block may be attributed to its depolarizing nature. Also, suxamethonium is hydrolysed rapidly by plasma cholinesterase and an overdose is usually used, which speeds the onset of block further without marked prolongation of its duration. This may explain our repeated failure to discover a new non-depolarizing neuromuscular blocking drug which can achieve the rapid onset of suxamethonium block.

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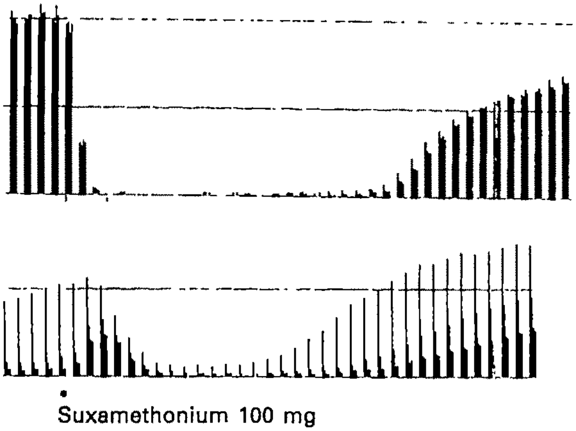

FIG. 1. Electromyographic response to ulnar nerve stimulation by train-of-four every 20 s, showing the neuromuscular block produced by suxamethonium 100 mg in one of the patients before (upper trace) and after vecuronium (lower trace).

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## MEASUREMENT OF TRANSTHORACIC ELECTRICAL IMPEDANCE

Sir,—A paper comparing the use of Ringer's acetate with 3% Dextran 70 for volume loading before Caesarean section appeared recently in *British Journal of Anaesthesia* [1]. One of the methods described in this paper was the estimation of extravascular lung water by the use of transthoracic electrical impedance (TEI) (also termed thoracic fluid index by the makers of the BoMed NCCOM3 used in this study). The authors were correct to stress that TEI is affected by both intra- and extravascular fluid. However, it must be remembered that the paper which they quoted showing a correlation between double dye-dilution and TEI estimation of lung water was carried out in an animal model in which the intravascular volume remained constant [2].

We wish to draw attention to one other factor which affects TEI and which differed significantly between the two groups of patients studied, namely the PCV. Increases in PCV result in an increase in the resistivity of blood [3] and this influence of PCV on TEI has been demonstrated in animal models [4]. Recently, we have investigated this relationship in humans, comparing a group of patients with polycythaemia rubra vera who had a mean PCV of 49.4% with a control group who had a mean PCV of 42.1%. The mean TEI in the first group was 31.25 Ω, which was significantly greater than that in the second group—27.5 Ω ($P < 0.05$) [5].

These observations may help to explain the "surprisingly increased response in TEI" noted by the authors. The influence of PCV clearly assumes greater importance with larger variations in PCV, seen, for example, after cardiac surgery.

Failure to understand the limitations of TEI in the estimation of lung water may explain why a technique that was well described more than 20 years ago has yet to find its way into routine clinical use.

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Sir,—Thank you for the opportunity to respond to the comments of Drs Thomas, Vohra and Pollard. We do agree that the change in intravascular volume as demonstrated by haemodilution of different magnitude in the two groups of treatment complicates the interpretation of transthoracic electrical impedance (TEI). However, as blood losses were similar in the two groups, the smaller PCV in the 3% Dextran group indicates that intravascular volume is larger after Dextran treatment than after Ringer's acetate. The decrease in TEI after Ringer's acetate, therefore, seems mainly to represent an increase in extravascular lung water. The decrease in resistivity of blood caused by decreased PCV as pointed out by Drs Thomas, Vohra and Pollard, would have affected Dextran-treated patients more, thereby decreasing TEI more in this group. However, only a moderate change was seen, in contrast with the more pronounced decrease in TEI after Ringer's acetate.

In summary, both the smaller PCV *per se* and the larger intravascular volume would have augmented a decrease in TEI in the Dextran-treated patients as a result of an increase in extravascular lung water. A more direct method for investigation of extravascular lung water would thus probably have resulted in even more pronounced differences between the two kinds of volume loading before extradural Caesarean section.

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## SURFACE ELECTRODE POSITION DURING ULNAR NERVE STIMULATION

Sir,—Although the recent paper by Kalli [1] on the effect of surface electrode position on evoked EMG response appears to be well designed, experience from our department is at variance with some of his results. Kalli reported a peak-to-peak amplitude of 8.5 mV when the evoked compound action potential (ECAP) was measured using the adductor pollicis muscle and the index finger (TD2) as the recording electrode pair. He found that the response of the first dorsal interosseous was significantly greater (12.5 mV) and hence preferred the latter muscle for clinical monitoring.

Using a study design and instrumentation that appeared to be similar to that of Kalli, we found that TD2 electrode placement produced a peak-to-peak amplitude of 13.1 (SEM 0.7) mV or 50% greater than the evoked response that Kalli recorded. However, a modest resting tension was applied to the thumb in all of our patients. In Kalli's investigation the arm to be studied was secured in a splint, but there was no mention of any preload applied to the thumb. As there is some evidence that preload can effect the ECAP [2], it would be helpful if Kalli could be a little more specific regarding the exact method used to secure the experimental hand and arm. If no resting tension on the thumb was used, Dr Kalli's conclusions on the usefulness of the adductor pollicis compared with the first dorsal interosseous may need to be re-examined.

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Sir,—I read with interest Dr Kopman's comments on evoked compound muscle action potential (ECAP) monitoring of muscle relaxation.

The aim of the recent study [1] was to compare the ECAP responses of different muscles of the hand. The hand was fixed in a neutral position on a splint, no pre-tension was applied to the thumb Increased hand muscle mass may have an impact on ECAP. Female patients with similar characteristics were selected to minimize interindividual variability. Depending on the methodology used in various studies, the results may vary.

In Dr Kopman's study [2], the responses were studied during nitrous oxide in oxygen anaesthesia and up to 15 min after barbiturate induction. In my study, ECAP were assessed from 30 to 60 min after induction during a steady isoflurane anaesthesia. Control recordings which were made 30 min apart did not show any time-related difference. Without further studies, it is unclear if different anaesthetic techniques have an effect on the recorded ECAP. However, it has been claimed that, at 10–20 min after induction, ECAP baseline drift may occur [3].

The thenar ECAP response may be affected significantly by the site of the indifferent recording electrode [4]. In the present study, when the indifferent electrode was moved from the second to the first finger, the adductor pollicis peak-to-peak amplitude decreased by 27%.

Preload applied to the thumb is an essential part of the mechanomyographic method of monitoring neuromuscular block. It has been recommended also to improve assessment of train-of-four [5]. Although ECAP and muscle contraction are different entities, a few reports have suggested that thumb position and pre-tension may affect thenar ECAP [2, 6, 7]. This subject has not been studied widely but, in a recently completed study, I analysed the effect of standard preload on adductor pollicis ECAP. Peak-to-peak amplitudes increased by 10% when a preload of 250 g was applied to the thumb. This implies that ECAP response of the adductor pollicis with the additional application of preload to the thumb was 76% of the response of the first dorsal interosseous muscle.

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# BOOK REVIEWS

*Clinical Anaesthesiology. Intensive Care: Developments and Controversies.* Edited by G. J. Dobb. Published by Baillière-Tindall, London. Pp. 613; indexed; illustrated. Price £22.50.

This multi-author book is one of a series which has dealt previously with various anaesthetic topics and is published three times yearly. This particular issue is devoted to recent intensive care developments and controversies. Despite the North American sounding title, the editor and all contributors are British (note the spelling of "*Anaesthesiology*") and many will be recognized by the readers.

Chapters of particular interest include the effects of sepsis on the heart and circulation, the mechanisms and prevention of nosocomial infections, perioperative management of patients with ischaemic heart disease and continuous methods of replacing renal function in patients with acute renal failure.

Intensive Care is a widely expanding specialty which is increasingly making greater demands upon the time and skills of anaesthetists—the recent College discussion regarding a Diploma in Intensive Therapy is witness to this. This book fills a gap between journals and established textbooks of Intensive Care in much the same way as the *Anaesthesia Review* series familiar to all Fellowship candidates. On the whole, all the chapters are well written and referenced, with clear illustrations. I believe it is a valuable book for both Consultants with Intensive Care commitments and the candidate for Part 3 of the Fellowship examination, and is to be recommended.

*M. J. Jones*

*Manuel d'Anesthésie Pédiatrique*, 1st Edn. Edited by C. Saint-Maurice, I. Murat and C. Ecoffey. Published by Editions Pradel, Paris. Pp. 437; indexed; illustrated. Price FF 390.

It has been a good year for textbooks of paediatric anaesthesia: the new volume from London and revised editions from North America are joined by this book. The three editors are from hospitals in the Paris region, the 25 authors from centres in France and Belgium.

The book is in four sections. The first discusses perinatal physiology, preparation of the child for anaesthesia, equipment and fluid balance. The second gives a detailed account of the pharmacology of anaesthetic drugs in children. The third provides a comprehensive account of anaesthesia for various operations, ranging from ENT and orthopaedic surgery to hepatic transplantation. This section includes a chapter on the management of burns. The final section is concerned with postoperative pain relief and regional analgesia. There is no chapter devoted to neonatal intensive care and resuscitation of the newborn is not discussed.

Not surprisingly, the book describes practice in Continental Europe, with greater emphasis on the use of benzodiazepines and rectal administration of drugs than is customary in Britain.

The book has many virtues. All chapters are concise and the references are well chosen and up-to-date. Where the recommended management is controversial, such as emergency surgery for congenital diaphragmatic hernia, the alternative approach is discussed. Some of the chapters on basic sciences are outstanding, and those on local blocks give a realistic appraisal of their limitations in paediatric practice.

Nevertheless, there are disappointments. The inclusion of a chapter on venous cannulation suggests that this book is intended for the trainee and occasional paediatric anaesthetist, yet the detailed section on congenital heart disease, surely a highly specialized field, is as long as those on orthopaedics, ENT and ophthalmology combined. The description of paediatric ventilators is very brief and the problems of capnography at high ventilatory frequencies and low tidal volumes are hardly mentioned.

Trainees soon learn that no single textbook can embody universal truth. This book is neither detailed nor comprehensive enough to be considered authoritative, but its merits make it a useful addition to recent publications on paediatric anaesthesia.

*H. F. Seeley*

*Anaesthesia for Day Case Surgery. Baillière's Clinical Anaesthesiology—International Practice and Research*, Vol. 4, No. 3. Edited by T. E. J. Healy. Published (1990) by Baillière-Tindall, London. Pp. 823; indexed; illustrated. Price £22.50.

With the burgeoning of day-case anaesthesia, many anaesthetists may be expected to undertake regular day-stay lists for the first time. This 217-page book, the latest in the series of *Baillière's Clinical Anaesthesiology*, would seem to respond to this change in clinical practice. The 11 chapters by different authors are: "Assessment of fitness for daycase surgery under general anaesthesia"; "Premedication for day case anaesthesia"; "General anaesthesia for day stay surgery"; "Muscle relaxants for day stay surgery"; "Local anaesthesia for day stay surgery"; "Recovery from day case anaesthesia"; "Paediatric day case anaesthesia"; "Psychological aspects of day care surgery for children"; "Requirements for a free standing day stay centre"; "The dental day case unit"; "Nursing the day stay patient".

I fear that the anaesthetist who turns to this book for answers to specific questions may be disappointed. Despite the erudite subjects covered, there is no discussion of gynaecological or ophthalmic day-stay units, so the problems of pain after laparoscopy or the relative merits of local eye blocks are not discussed. When topics are covered, the advice provided is not always helpful: for example, in the discussion on caudal block one might expect a dosage regimen but, instead, the reader is referred to the work of Armitage; trimeprazine is recommended as a premedication in a dose varying from 0.25–0 45 and 0.3–0.4 mg $kg^{-1}$ (p. 647) to 4 mg $kg^{-1}$ (p. 656) in the same chapter.

There are many errors: the meaning of anterograde and retrograde amnesia is reversed (p. 641); droperidol is said to produce amnesia in a dose of 0.25–0.5 mg (p. 660); the neuromuscular blocker, Org 9426 is said to be five times less potent than vecuronium, but the $ED_{95}$ of 0.028 mg $kg^{-1}$ appears to show that it is more potent.

This book lacks cohesion. The first pages of many of the chapters repeat the same basic principles. English terminology is used as standard, but acetaminophen appears on p. 718 instead of paracetamol. Only in the middle of the dental chapter is there a detailed specification for monitoring in day case anaesthesia.

Although I found the chapters on General Anaesthesia, Muscle Relaxants and Assessment of Recovery interesting, in general this book was disappointing and cannot be recommended.

*R. H. James*

*Monitoring in Anesthesia and Critical Care Medicine*, 2nd Edn. Edited by C. D. Blitt. Published by Churchill Livingstone, New York. Pp. 903; illustrated. Price £75.00.

The first impression of this book is one of competence and thoroughness. It consists of 33 chapters in six sections. The first section deals with the general principles of monitoring and gives a useful introduction to the problems and pitfalls of the subject. In addition, it gives a historical overview of the development of monitoring in the field of anaesthesia and reminds the reader of the basic monitoring skills an anaesthetist has to acquire in case the electronics fail. A chapter on the philosophy of monitoring may not appeal to British and European readership, but is possibly aimed at the American market.

The following sections deal with monitoring the cardiovascular, respiratory and central nervous systems, respectively. It is refreshing to read a review of the benefits of pulmonary artery catheterization by authorities such as H. J. C. Swan and W. Ganz; this is followed by more detailed analysis of the physiological importance and complications of this mode of monitoring.

In a later chapter, on monitoring in the Critical Care Unit, further information is provided on the use of pulmonary artery catheterization for assessing oxygen transport and oxygen consumption, and the concept of supply dependent oxygen uptake is introduced. The section on monitoring the respiratory system is comprehensive yet concise, and again the choice of author made it a particular pleasure to read.

In the third section the emphasis is on EEG, evoked potential and intracranial pressure monitoring. The last chapter of this section is dedicated to assessment of anaesthetic depth and, although succinct, gives a readable introduction to the subject for the uninitiated.

The section on miscellaneous monitoring deals with temperature, urine output, miscellaneous blood variables, the anaesthetic delivery system and the neuromuscular junction. The last section introduces monitoring specific to various subspecialties such as neuro, cardiac, obstetric and paediatric anaesthesia and critical care medicine.

Throughout the book may be found the same high standards of thorough review and introduction to the latest technology and in-depth literature survey. From a British viewpoint, this book should be part of every anaesthetist's library, both trainee and consultant. One minor criticism is that not enough emphasis has been placed on measuring and monitoring regional blood flow. Although Duplex doppler ultrasound is mentioned in the last chapter, its application to renal and splanchnic flow measurement is not mentioned; this is an area which is gaining importance in anaesthesia and intensive care. However, the book makes enjoyable reading and makes one aware of the possibilities in monitoring which, in the U.K., seem to be almost unattainable in the present financial climate.

*W. J. Kox*

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